



UNITED STATES DISTRICT COURT  
SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE, INCORPORATED, )

Plaintiff, )

vs. )

VYSIS, INC., )

Defendant. )

No. 99CV 2668H (AJB)

**CERTIFIED**

**COPY**

DEPOSITION OF KARY B. MULLIS, Ph.D.

Newport-Beach, California

Friday, November 2, 2001

Reported by:  
LINDA L. SILVER  
CSR No. 9915  
JOB No. 141508

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 Plaintiff, )  
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 vs. ) No. 99CV 2668H (AJB)  
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 VYSIS, INC., )  
 )  
 Defendant. )  
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Deposition of KARY B. MULLIS, Ph.D.,  
taken on behalf of Defendant, at 1107  
Jamboree Road, The Palm Room, Newport Beach,  
California, beginning at 9:50 a.m. and ending  
at 2:39 p.m. on Friday, November 2, 2001,  
before LINDA L. SILVER, Certified Shorthand  
Reporter No. 9915.

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1 Newport Beach, California, Friday, November 2, 2001

2 9:50 a.m. - 2:39 p.m.

3  
4 THE VIDEOGRAPHER: Good morning. Here begins  
5 videotape number one in the deposition of Kary B. Mullis  
9:29 6 in the matter of Gen-Probe, Incorporated versus Vysis,  
9:50 7 Incorporated in the U.S. District Court Southern  
8 District of California, the case number of which is  
9 99CV-2668H (AJB).

9:51 10 Today's date is November 2nd, 2001. The time  
11 is 9:50 a.m. This deposition is being taken at 1107  
12 Jamboree Road, Newport Beach, California and was made at  
13 the request of L. Scott Burwell of the Law Offices of  
14 Finnegan, Henderson, Farabow, Garrett & Dunner.

15 The videographer is Mike Henry with Esquire  
16 Deposition Services of Washington D.C.

17 Would counsel and all present please identify  
18 yourselves and state whom you represent.

19 MR. LIPSEY: Charles Lipsey with Finnegan,  
9:51 20 Henderson, Farabow, Garrett & Dunner representing the  
21 defendant Vysis, Incorporated, and joined by my  
22 colleague Scott Burwell.

23 MR. SWINTON: Steve Swinton on behalf of  
24 Gen-Probe.

25 THE VIDEOGRAPHER: Thank you.

7



1                   Would the court reporter please administer the  
2 oath to the witness.

3  
4                   KARY B. MULLIS, Ph.D.,  
5 having been first duly sworn, was examined and testified  
6 as follows:

7  
8                   EXAMINATION

9 BY MR. LIPSEY:

10           Q     Good morning.

11           A     Good morning.

12           Q     Would you state your full name and residential  
13 address for the record, please.

14           A     Kary B. Mullis, and 919 Bayside Drive,  
9:52 15 Apartment O-4, Newport Beach, California, 92660.

16           Q     By whom are you currently employed?

17           A     By a number of different people. I do a lot of  
18 consulting, and also I am a traveling lecturer, so there  
19 are a whole bunch of different people that end up paying  
9:52 20 me at any one time.

21           Q     You're basically self-employed; is that right?

22           A     Yes.

23           Q     I gather you perform consulting services for a  
24 number of companies; is that right?

25           A     Yes. Mainly what I do now is give lectures,

1 which is a lot more fun.

2 Q You're appearing here today as an expert  
3 witness on behalf of Gen-Probe; is that right?

4 A Yes.

9:53

5 Q When were you retained as an expert witness for  
6 Gen-Probe?

7 A I think it was about a year ago, year and a  
8 half ago, something like that. I actually can look that  
9 up if you need to know.

10 Q No, general time frame is close enough.

11 How did you come to be retained as an expert  
12 for Gen-Probe?

13 A I -- my recollection is that Bill Bowen called  
14 me on the telephone, and I'm not sure how he got my  
15 phone number, but it's not hard to find.

16 Q Did you know Mr. Bowen?

17 A I didn't know him prior to that.

9:53

18 Q Had you had any connection with Gen-Probe prior  
19 to that?

20 A I can't recall ever having any specific  
21 connection with them. I certainly knew people in San  
22 Diego that worked there whose names I could probably dig  
23 up if I needed to, but I've never -- I never worked for  
24 them, and I don't think I ever did any kind of legal  
25 consulting or biochemical consulting for them.

9

1 Q Did you know Dan Kacian?

2 A The name doesn't sound real familiar. I don't  
9:54 3 think I knew him.

4 Q Had you had any connections with Chiron prior  
5 to the time you were retained as an expert in this case?

6 A Let's see, I think I must have consulted for  
7 them at least on one occasion, and I was quite familiar  
8 with Ed Penhope, the president of Chiron and one of the  
9 founders, and Mickey Urdea. They were across the street  
10 from me. When I worked at Cetus, Chiron was formed, and  
9:54 11 their offices and laboratories were right across the  
12 street from us. So I had a good bit of interaction with  
13 them for a while while I was still working at Cetus.

14 Q When is the last time you -- well, are you on  
15 retainer or any such arrangement with Chiron?

16 A With Chiron, no.

17 Q When was the last time you performed any  
18 consulting services for Chiron?

19 A It would have been probably in the like 1988,  
9:55 20 somewhere around there. And I'm not really certain. I  
21 know I went there, gave lectures. Whether they paid me  
22 or not, I can't remember right now. They would have to  
23 now. But I think there was like a period when I maybe  
24 consulted with Mickey Urdea there a couple of times.

25 Q Have you had any consulting arrangements with

10

1 a Japanese company, Chugai Pharmaceuticals?

2 A Let's see, the question is whether I've been a  
9:55 3 consultant for them?

4 Q Yes.

5 A No, I've not consulted for them, but a company  
6 here that I -- here in Newport Beach or actually here in  
7 Irvine county called Burstein Labs had some corporate  
8 interaction with them. Well, it was being explored and  
9 I think Chugai backed out of it, but I met with some  
10 Chugai people in the last year. Not with anything to do  
11 with this case. It was something entirely different.

9:56 12 Q Okay. Have you had any consulting arrangements  
13 with the German company Bayer or any of its associated  
14 companies?

15 A I'm not certain about its associated  
16 companies, but not directly -- I mean, I've never been  
17 hired by somebody that called themselves Bayer. They  
18 might have a lot of different little outfits. I've  
19 consulted for a lot of little companies, usually just  
9:56 20 one or two times, so it's a whole long list of companies  
21 that I've consulted for.

22 Q Do you have an ownership or equity position in  
23 any company now?

24 A I have a lot of stock options for this company  
25 Burstein Technologies that I mentioned that had the

1 interaction with Chugai, and -- you mean like sometimes  
2 trying to make money and losing it, that kind of stock?  
9:57 3 I've certainly bought and sold, usually buying high and  
4 selling low. But right now I probably have a number of  
5 shares in, you know, a whole slew of little biotech  
6 companies, but Gen-Probe is not one of them. And I  
7 don't know if I've ever owned any of their stock or even  
8 if it's -- I assume they're a publicly held company.

9 Q What is the business of the company you  
10 mentioned, Burstein?

11 A Burstein, they're developing a diagnostic  
9:57 12 system based on optical disk drives, and it's like a  
13 general diagnostic system. The thing that I -- when I  
14 was working there actively, I -- in my lab we were  
15 developing a way to look at bacteria in urine samples.

16 We were also developing amplification  
17 techniques, more basically PCR-type techniques that  
9:58 18 could be done on a disk inside of a disk drive.

19 Q Did that technology combine a target capture  
20 step with amplification?

21 A We never really -- we never got it to the point  
22 where we would have had to -- never got to the point we  
23 were working with real samples where we might have had  
24 to pull some DNA out of it. We were working with, like,  
9:58 25 laboratory samples that already had been cleaned. We

1 were basically just working with the process of how do  
2 you do an amplification on a spinning optical disk.

3 Q Okay. I saw from your CV that you had had some  
4 experience testifying in what appeared to be criminal  
5 cases. Have you ever testified in a civil case before?

6 A Yes.

7 Q Any of those patent cases?

8 A There seems like it's an ongoing patent case  
9 with regard to PCR just about everywhere all the time,  
10 and with, let's see -- at like the company like Hoffman  
11 La Roche, I've testified from them. Also for Applied  
12 Biosystems, they have PCR kind of issues occasionally.  
13 Perkin-Elmer.

14 Q In those cases, are you testifying as a fact  
15 witness about your work with PCR, or were you testifying  
16 as an expert as you are in this case?

17 A Generally --

18 MR. SWINTON: I'm sorry, Dr. Mullis, from time  
19 to time I may need to interrupt only to assert an  
20 objection. I'm not intending to stop you from giving  
21 the answer, but just so the court reporter doesn't have  
22 to fight over us.

23 The objection I was going to assert is that it  
24 may call for you to speculate and calls for a legal  
25 conclusion about the actual nature of your testimony.

1 That's my objection for the record only. Please proceed  
2 to answer.

3 THE WITNESS: Okay. I as far as I know, not  
4 being a lawyer, I just believe what they tell me, I have  
5 done both. I mean, I've been -- I have some idea of  
6 what the difference is, but I mean, you know, PCR court  
7 cases have drug out for years and years, and I get  
8 involved in them in different ways, but I think at least  
9 two of them have been as a fact witness.

10 BY MR. LIPSEY:

11 Q Okay, but you believe in some of them you've  
12 been an expert also?

13 A Yes, and I think the bulk of the time that I've  
14 been in courtroom situations, it's been as an expert.  
15 My idea of what that is is -- may be probably not what  
16 it is, but I think --

17 Q I'd love to take up your time asking for a list  
18 of those instances where you've testified.

19 Mr. Swinton, perhaps could you agree to provide  
20 us with a list of the instances where Dr. Mullis has  
21 testified and that way we don't have to take up his  
22 time?

23 MR. SWINTON: If you cut short the 7 hours,  
24 I'll be happy to do that. I'm not sure I want to  
25 accommodate just to extend this out for more time but to

14

1 the extent we can, we'll try.

2 THE WITNESS: I think maybe my CV that was sent  
3 to you doesn't contain all of that, but I thought there  
4 was one section of it that talked about testifying in  
5 various -- my wife, I think sent that, and there is  
6 different versions of it, but --

7 MR. LIPSEY: Well, why don't we mark for  
8 identification as Defendant's Deposition Exhibit 197 a  
10:01 9 copy of the CV of Dr. Mullis that we have, and if it's  
10 not the right one, then we'll find out soon enough.

11 (Defendant's Exhibit 197 was marked for  
12 identification by the court reporter.)

13 BY MR. LIPSEY:

14 Q I guess just for the record, is Defendant's  
15 Exhibit 197 a copy of your CV?

16 A Yes.

17 Q And to the extent it contains information, is  
10:02 18 it your brief that it's true and accurate?

19 A Yes.

20 Q Okay. Now, can you tell from examining it  
21 whether it lists the instances in which you have  
22 previously testified?

23 A You know, I think that what has been done here  
24 is the companies that I've maybe -- you know, like it  
25 mentions like Applied Biosystems here, Orrick,

15



1 Herrington and Sutcliffe:PE Applied Biosystems. This is  
2 in the part that is called "Private Consultant," and I  
3 think I've put those things that were noncriminal things  
4 in with those companies that I consulted for.

5 That's what I've -- it's -- it doesn't, for  
6 instance, say, McCutchen, Doyle, Enersen & Brown, San  
7 Francisco, it doesn't say that was a legal case, but  
8 that's what that was. There is a number of those like  
9 Orrick, Herrington, Sutcliffe, obviously that was one of  
10 those, Perkin Elmer, Foster City. I've had --

11 Q Is it your belief you have a list of the actual  
12 cases in which you've testified someplace?

13 A I have had files and stuff on that, and I could  
14 prepare such a list if you wanted to see that. I guess  
15 I didn't make that specific here.

16 MR. LIPSEY: Okay. Counsel, rather than take  
17 Dr. Mullis's time to do that, I would renew my request  
18 that you provide us with a list of the cases in which  
19 Dr. Mullis has previously testified.

20 MR. SWINTON: Beyond that that is required in  
21 the disclosure? I just want to make sure I know what  
22 you're asking for.

23 MR. LIPSEY: I'd like the complete list.

24 MR. SWINTON: If we can reasonably do it, I'll  
25 endeavor to do that.

1 MR. LIPSEY: I'd like the reporter to mark for  
2 identification as Defendant's Deposition Exhibit 198 a  
3 copy of a document entitled "Expert Report of Dr. Kary  
10:04 4 B. Mullis Pursuant to Fed.R.Civ.P.26."

5 For efficiency, let's go ahead and mark as  
6 Defendant's Deposition Exhibit 199 a copy of a document  
7 entitled "Declaration of Dr. Kary B. Mullis in Support  
8 of Gen-Probe Incorporated's Motion for Partial Summary  
9 Judgment of Noninfringement Under the Doctrine of  
10:04 10 Equivalents."

11 (Defendant's Exhibits 198 - 199 were marked  
12 for identification by the court reporter.)

13 BY MR. LIPSEY:

14 Q Just for the record, Dr. Mullis, is Defendant's  
15 Deposition Exhibit 198 a copy of the expert report you  
16 have submitted in connection with this case?

17 A It appears to be.

18 Q Now, I note from the last page of the report  
10:05 19 itself, page 20, that you signed it on September 26,  
20 2001; is that right?

21 A Yes.

22 Q And I note from page 16 of Defendant's  
23 Deposition Exhibit 199, which is a declaration of yours,  
24 that you signed it on September 26, 2001 also; is that  
10:05 25 right?

1           A    I'll take your word for it unless you want --  
2           yes, September 26, that's right.

3           Q    Without trying to belabor the point, is it your  
4           understanding that the substance of your report and the  
5           substance of your declaration both executed on September  
6           26, 2001 is the same?

7           A    Is the substance of the two the same?

10:06 8           Q    Right.

9           MR. SWINTON:  Objection; the documents speak  
10          for themselves.  Notwithstanding, the documents being  
11          the best evidence, go ahead and answer.

12          THE WITNESS:  I don't think there is any  
13          differences of like factual or speculative kind of stuff  
14          in them.  I think they cover the same kind of material.

15          BY MR. LIPSEY:

16          Q    And is it your recollection that they express  
17          basically the same opinions?

18          MR. SWINTON:  Same objection.

19          THE WITNESS:  It is -- you know, without your  
20          being a little -- there is a lot of opinions in there,  
10:06 21          and I think that my opinions on matters in this case  
22          haven't changed between the one and the other.  They  
23          certainly should reflect the same general ideas.

24          BY MR. LIPSEY:

25          Q    I guess I was hoping to short circuit the whole

1 process, because it looks to an outsider as if the two  
2 documents were prepared together, and one was in the  
3 form of a report and one was in the form of an  
4 affidavit.

5 Is it your recollection that is the way it was  
6 done?

7 A Yes, yes.

8 Q Now, referring to your report, Defendant's  
10:07 9 Exhibit 198, can you describe the process by which that  
10 report was prepared.

11 A There were a lot of conversations with Bill  
12 Bowen. There were some documents -- he -- I sent him  
13 some written material. He sent me some. We went -- you  
14 know, he incorporated the stuff I had sent him into a  
10:07 15 sort of a format that looked more like a lawyer had  
16 written it, and we just -- you know, we worked on it  
17 together that way.

18 And in every case, it would come back to me for  
19 like the final approval of how he described -- and in a  
20 lot of cases he just used my words verbatim, and in some  
21 places he would, like describe things that we talked  
22 about in his own way, but in a way that I agreed with.

10:08 23 Q Do you have the draft materials that were used  
24 in the process you just described?

25 A Yeah, I think I have those -- they're like -- I

10:08

1 think I do. Do you want to see them?

2 Q Sure.

3 A I think you've probably got them already in the  
4 things that I sent to Bill.

5 Q Okay. I see now that you have a folder of  
6 things that you brought with you. Is all of that  
7 ultimately intended for us?

10:09

8 A If you want to see it. I didn't bring  
9 everything I've ever read in my life, which is what you  
10 asked me to do, and I thought that was rather rude, the  
11 way that you stated the things that I should bring was  
12 absolutely absurd or somebody did. But these are the  
13 things that I think of as being pertinent to this  
14 particular case in terms of things that I've had some  
15 input in. I figure you've got your own copies of the  
16 patents and all of the literature and stuff.

10:09

17 MR. LIPSEY: Okay. Well, with your permission,  
18 Counsel, if the witness can share that with us, we'll  
19 try to look at it at a break and try to minimize the  
20 amount of time we take.

21 Thank you.

22 Q Okay. I would like to find out what materials  
23 you considered in formulating the opinions that you've  
24 expressed in your expert report, Exhibit 198.

10:10

25 A Well, certainly I was furnished a copy of the

20

10:10

1 patent, the `338 patent. I was -- and I think I also  
2 looked at fairly lengthy reports from, I think this  
3 man's name is Persing, his opinions. Specific things, I  
4 mean, it's hard to say where, you know, something starts  
5 being specific.

6 I've had a long history in the area of  
7 amplification, so occasionally I look at articles and  
8 things that I don't really copy and say I've now looked  
9 at this article, but, I mean, I have a general awareness  
10 of the literature for the past 20 years in the area of  
11 amplification, and I certainly refer to that, if not  
12 specifically article by article, I mean, that's my  
13 background.

J:11

14 Q Can you recall any articles you specifically  
15 consulted?

16 A Not -- I can't recall any specific ones.

17 Q Were there any other materials --

18 A I mean, I've looked at my own patents in this  
19 area. I remember pulling those out and just looking at  
20 what was going on back in -- trying to remember what was  
21 going on in 1985, that kind of thing, and one way to do  
22 that is to go back and look at things that I'd written  
23 during that period. So I would have to say that.

10:11

24 Q That's the sort of thing that I'm interested  
25 in. So you looked at your own patents?

21

1 A Um-hum.

2 Q Did you look at any of your own articles from  
3 that time?

4 A Yes.

5 Q Can you identify to the best extent that you  
6 can what those were?

7 A I think I could probably do it better if I was  
8 looking at my CV here. There is a list of my patents in  
9 the CV, and I didn't look at all of these, but any -- I  
10:12 10 certainly --

11 Q Stop right there. Do you remember which  
12 patents you looked at?

13 A The `202, the one that we talked about, the PCR  
14 patent called the `202.

15 Q Okay. Any others?

16 A And I think the `198, I believe those are the  
17 numbers on it. No, I'm sorry, it's the `195. The `202  
18 and `195. U.S. 4,683,202 and U.S. 4,683,195. I  
19 remember looking at those just to see in my memory what  
10:12 20 was going on there.

21 Q Before we leave the patents, were there any of  
22 the others that are listed there in your CV, Defendant's  
23 Exhibit 197, that you remember looking at in connection  
24 with preparing your report?

25 A I don't remember looking at any other ones

1 specifically, but I may have. I don't remember not -- I  
2 mean, I have a box full of them, and I probably looked  
3 at them, if they had any relevance, and some of them  
4 did.

10:13

5 Q But like what?

6 A Well, I was trying to figure out why -- why  
7 this particular -- this `388 (sic) patent never got  
8 applied for or issued, and I was trying to understand  
9 what sort of the basis of the -- what was the original  
10 basis of that patent and how did it get to be the way it  
11 was sort of, and I think part of that was looking back  
12 at what things had already been patented in that area at  
13 the time of the `388's being issued.

J:13

14 Q Did you find in your review that the subject  
15 matter of the `338 patent had already been patented by  
16 somebody else?

17 MR. SWINTON: Calls for a legal conclusion,  
18 beyond the scope of his opinions.

19 THE WITNESS: I would go with that. I couldn't  
20 understand why somebody would have applied for it, I  
21 guess. I mean, it's the same thing. I didn't see any  
22 kind of real original material in the `388 to tell you  
23 the truth.

10:14

24 BY MR. LIPSEY: ,

25 Q I guess my specific question is, in your

23



1 review, did you find a patent that had been issued to  
2 somebody else on the subject matter of the '338 patent?

10:14

3 MR. SWINTON: Same objection; legal conclusion,  
4 beyond the scope of his opinions.

5 THE WITNESS: There were a lot of commonly used  
6 procedures that I was -- I was familiar with and where I  
7 could have probably found at least literature referring  
8 to. The things like, you know, mRNA and cloning stuff  
9 like that that I think bears on the patentability of the  
10 material in the '388 that I could have found places in  
11 literature that -- because my knowledge of that stuff is  
12 sort of general. I didn't have to go to specific spots  
13 and say, "This particular article or this claim of this  
14 patent is talking about something that seems to be  
15 patented in the '388." I didn't go to that level of  
16 detail.

10:15

17 BY MR. LIPSEY:

10:15

18 Q Okay. We were getting back to the materials  
19 that you had reviewed in preparing your opinion, and I  
20 think you said you had looked at some articles also, and  
21 you were about to look in your CV, Defendant's Exhibit  
22 197, to see if we could figure out which ones those  
23 were.

24 A Things like -- well, there are quite a few of  
25 them in here, and I don't have any specific ones marked

24

1 that I specifically referred to, but, you know, articles  
7:16 2 like Mullis, Faloona, Scharf, Saiki, Horn and Erlich,  
3 Quantitative Biology 51. It was like in 1986. It was  
4 like an early description of PCR, which I think I just  
5 looked through that to see --

6 Again, you know, with the idea in mind of  
7 saying what was happening in 1986 that sort of formed  
8 the context for this patent having been issued. I mean,  
9 I was kind of puzzled why the thing was issued, and I  
10:16 10 was looking back saying how is it that some patent  
11 examiner would think these things weren't already being  
12 done in some way or other? It was not my business to do  
13 that because I'm not a patent lawyer, but I was  
14 curious.

15 Q So you've identified the Mullis, Faloona and  
16 others article in --

17 A Cold Spring Harbor Symposium article in  
10:17 18 Quantitative Biology 51. That was like a real early PCR  
19 publication, and there are several others around in that  
20 same time period that I'm sure I looked at.

21 Q Do you recall specifically which those were?

22 A Well, if -- they're like -- there is one in  
23 Nature 324 : 6093 (1986).

10:17 24 Q That's the next reference on that page of your  
25 CV?

1 A Yes.

2 Q Okay. Any others?

3 A I think I probably looked at this Kwok paper.  
4 It was the Journal of Virology 61 : 1690 (1987). I  
5 think I looked at that. That was a paper where the --  
10:18 6 there was some need for some prepurification there of  
7 samples that had very low levels of HIV.

8 Q Any others?

9 A I wouldn't specifically point to any others.  
10 Like I said, I have boxes of papers, you know, and when  
11 I'm working on something like this, I might leaf through  
12 a whole lot of them to find specific things, but I don't  
10:18 13 make a record necessarily of which ones I've looked at.

14 Q So you've identified for me the ones that you  
15 remember looking at; is that true?

16 A Yes.

17 Q While we're on this page of your CV, which of  
18 these articles is the first publication describing PCR?

19 A That's the Science 230 (1985), the paper that  
20 starts off with Saiki's name.

21 Q Do you recall when in 1985 that was published?

10:19 22 A Right around Christmas.

23 Q Okay. Were there any other materials that you  
24 reviewed in formulating the opinions expressed in your  
25 expert report in this case?

1 A I can't remember any specific ones.

2 Q Did you have the expert reports of any  
3 witnesses other than Dr. Persing?

4 A You know, I think there were. I think there  
5 was a packet that had some -- yeah, there was some other  
10:19 6 expert, I think, working for Gen-Probe, and I can't  
7 recall that person's name, but as I remember at some  
8 point seeing like his response to Persing. And I should  
9 be able to recall his name, but I can't.

10 Q Just to run through some of them, Harpold, is  
11 that the name? Or Falkinham?

10:20 12 A Falkinham sounds right.

13 Q Falkinham. Okay. But you don't recall having  
14 a report by Dr. Harpold; is that right?

15 A I don't specifically recall that one.

16 Q Any other expert reports -- and I would include  
17 in there draft expert reports so that there is no  
18 ambiguity -- from any of the other witnesses that you  
19 had and considered in preparing your opinion?

20 A I can't recall any others specifically.

21 Q Were there any other materials that you  
10:20 22 reviewed or considered in connection with preparing your  
23 report, other than those you've identified to me?

24 A I can't remember any others.

25 Q How long did this process of preparing your

1 report take?

10:21 2 A I think it was -- probably went on for a matter  
3 of months. You know, when we first started sending back  
4 a -- I don't remember when I first sent Bill like two or  
5 three pages of my comments about the thing, when that  
6 first happened, but I would sort of consider that the  
7 beginning, and I might be able to find it. If you give  
8 me back all of those papers, I can look at the dates of  
9 some times when I sent him a bill. I might be able to  
10 figure out from that when the first time --

11 Q Sure, I'll hand back the collection of papers.

10:21 12 A It's somewhere in here. I thought it was in  
10:22 13 here.

14 No, you know, I was thinking this might contain  
15 that information, but this starts September the 17th,  
16 2001, and I'm certain this was going on long before  
10:22 17 that. This is the last sort of invoice that my wife  
18 prepared for Bill Bowen, and I thought it covered the  
19 whole time, but it didn't. So I don't know exactly when  
20 that first stuff started going back and forth. It was a  
21 long process, I remember that. Nobody seemed to be in a  
22 rush either.

23 Q Thank you.

10:23 24 How much time in the aggregate have you spent  
25 on this case?

1           A    I would say somewhere around maybe three to  
2 five days, that's eight hours spread out over a long  
3 period of time. I'm guessing there, but I think that's  
4 about right. I've been traveling a lot and coming back  
10:23 5 to this, and, you know, it has just happened  
6 periodically, so I'm not really sure.

7           Q    I think I saw in your expert report you're  
8 charging a fee of \$5,000 a day; is that correct?

9           A    For doing a deposition. Maybe it's \$5,000 a  
10 day for even working on it. I'm not certain. I thought  
11 it was 4, but maybe it's 5.

12          Q    Okay. So --

13          A    I have a very efficient wife/manager who takes  
14 care of those things.

15          Q    It's \$4- or \$5,000 a day for work other than  
10:24 16 testifying, and \$5,000 a day to testify; is that right?

17          A    Right. It may be that she's raised me up to 5  
18 for working.

19          Q    Do you know what criteria she uses for  
20 determining what your daily rate is?

21          A    Well, whatever the traffic will bear. I'm  
22 traveling around the world now giving lectures, and  
10:24 23 that's where I start, just to give a lecture, and this  
24 takes more time actually, and it's not nearly as much  
25 fun. I'm not trying to get a lot of this particular

1 kind of work by lowering the price.

2 Q So you're not the low cost provider of expert  
3 opinion; is that right?

4 A That's right. I'm not interested in bulk  
5 testimony.

6 Q Do you prorate that rate, or is that what you  
7 charge for any day on which you work on the case?

8 A No, that's -- that's for, like I said, an  
10:25 9 eight-hour day.

10 Q What, if anything, have you done to prepare for  
11 this deposition today?

12 A I read over the materials that I had provided  
13 Bill already and the things that had been sort of  
14 finalized like these documents. I last night read over  
10:25 15 some -- let's see, it was like a response. There was a  
16 nice little thing which is probably in that folder I  
17 gave you where the positions of Vysis and Gen-Probe are  
18 sort of matched against each other, and it's kind of an  
19 outline. I looked fairly carefully at that.

20 Q Anything else?

21 A I guess, I don't think anything specifically  
10:26 22 that I recall. This would have been like yesterday.

23 Q Okay. How much time did you spend yesterday?

24 A I think I spent about four hours.

25 Q Okay. Did you spend any time before yesterday

30

1 getting ready for the deposition?

2 A I think the day before yesterday I spent about  
3 an hour.

4 Q Any time before that?

5 A And I think previous to that it goes back into  
10:26 6 September or something.

7 Q Did you have any meetings or telephone  
8 conversations regarding preparation for this deposition?

9 A Very brief with Steve, probably two days ago.  
10 Not really terribly substantive. Most of the  
11 substantive comes by e-mail and, you know, documents.

12 Q What had you gotten by way of e-mail?

10:27 13 A Well, that's, like yesterday, that little thing  
14 I was talking about that is in there, it's an outline.  
15 The one thing that I kind of recall is sort of a  
16 structured looking page with little boxes saying here is  
17 what Vysis is saying and here is what Gen-Probe is  
18 saying on various issues.

19 Q That's something that you got from Gen-Probe's  
20 lawyers?

21 A Yes.

22 Q Anything else that came by e-mail?

23 A There were a number of documents. There was  
24 like a -- I can't remember what the names of them are.  
25 I think they're in that stack there.



1 Q Okay. By the stack, you mean the materials  
2 that you brought with you this morning?

9:27

3 A The stuff I gave you in that folder, I believe,  
4 is all of the things.

5 Q Any other -- how long did your meeting with  
6 Mr. Swinton last?

7 A You mean the telephone conversation?

8 Q Oh, I'm sorry, yes, the telephone  
9 conversation.

10 A I talked to him also this morning before we  
11 came over here, but the telephone conversation was very  
12 brief.

13 Q Okay. Was anybody else on the phone?

14 A No.

15 Q How long did you meet this morning with  
16 Mr. Swinton?

10:28

17 A I think he got there a little after 8:00, so we  
18 were probably sitting there for about an hour before we  
19 came over here.

20 Q Did you review any documents this morning in  
21 preparing to testify?

22 A I was looking at some of this -- I had them  
23 spread out on my table from last night, and they were  
24 there. We didn't study any one of them in particular,  
25 but we just talked mostly.

32

1 Q But the ones that you had before you were the  
2 ones in the folder that you brought with you this  
3 morning?

4 A Yes.

5 Q Were there any others?

10:28 6 A No, I brought everything that was there on the  
7 table.

8 Q Now, are there -- what issues were you asked to  
9 consider as an expert in connection with this case?

10 A I think in general -- most of the issues that I  
10:29 11 have been considering, I assume it's because I was  
12 asked, have to do with what is sort of what do you mean  
13 by specific and non-specific amplifications and how can  
14 you compare those, you know, in reasonable ways. I  
15 think that was -- that's the crux of the whole thing,  
16 well, what is the --

17 Although, I can remember when reading that  
18 original patent, I thought of a lot of different things  
19 in there like prepurification of samples by various  
10:29 20 methods, what that does and what it doesn't do. So the  
21 issue of specificity, I think has been the uppermost.

22 Q Okay. I gather you understand you were asked  
23 to express an opinion on the issue of infringement in  
24 this case; is that right?

25 A Well, putting it that -- I certainly did

10:30 1 express opinions, I think from time to time. But I  
2 don't remember being -- was I supposed to -- I think  
3 that's kind of a legal thing, isn't it, to say whether  
4 there is infringement or not? I don't usually get asked  
5 that kind of thing, but I certainly have mentioned  
6 that. I mean, it's not beyond me to see what is  
7 obviously an infringement and what is not, but the  
8 details I might get a little confused about.

9 Q Let me try using a different word. Is it your  
10 understanding you were asked to express an opinion as to  
10:30 11 what was and was not covered by the claims of the '338  
12 patent?

13 A Yes.

14 Q Were you asked to express opinions on any other  
15 issues?

16 A Any other issues besides what was covered by  
17 the patent claims of the '338?

18 Q Right.

19 A For example, give me -- what would you consider  
20 another issue?

21 Q Were you asked to express an opinion as to  
22 whether the subject matter claimed in the '338 patent  
10:31 23 was either novel or non-obvious?

24 A I think I probably was -- there were a lot of  
25 discussions about that. Whether I was specifically

1 asked that, I'm not sure, but I think I made some  
2 remarks in written form that you've got in that purple  
3 folder relative to that.

10:31

4 Q Okay. But none of those remarks found their  
5 way into your expert report, which is Exhibit 198,  
6 correct?

7 A Well, I'd have to look through it to see  
8 whether they did, but I think all -- I mean, that was  
9 the purpose of the whole thing, right?

10 Q You tell me.

11 A Well, it seems like that was what most of this  
12 was about. You want me to look through this Exhibit 199  
13 and see if I can find anything relevant to whether there  
14 was any original content in the `388 or something like  
15 that? Is that what you're asking?

10:32

16 Q I'm asking whether you expressed in your report  
17 an opinion as to the novelty or non-obviousness of the  
18 subject matter claimed in the `338 patent, and if you  
19 did, I'd like to know where it is.

20 A Okay, well, let's see, of the novelty of the  
21 `388?

22 MR. SWINTON: Objection; calls for a legal  
23 conclusion.

24 BY MR. LIPSEY:

25 Q Well, let me try to cut through it a little

35

1 bit.

10:32

2 You've got a bunch of patents yourself, right,  
3 Dr. Mullis?

4 A Yes.

5 Q And those patents have been involved in  
6 litigation for years, right?

7 A Yes.

8 Q And you've been involved, at least  
9 peripherally, in that litigation for years, correct?

10 A Right.

11 Q And you understood that in patent litigation  
12 that one of the issues involved is whether or not the  
13 party charged with infringement is infringing the  
14 patent, right?

15 A Yes.

16 Q And you understood that an issue that can arise  
17 in patent litigation goes to validity of the patent,  
18 right?

10:33

19 A Actually, I didn't know that until this  
20 morning. I wasn't certain. I thought those were two  
21 separate issues. I thought the one idea was whether  
22 somebody is infringing a patent, assuming that the  
23 patent is, in fact, valid, and that would be a separate  
24 legal issue, I thought, to challenge the validity of the  
25 patent. I was told this morning, no, that those can

36

1 happen at the same time.

2 Q But was it your understanding that in your  
3 report you were expressing opinions on whether or not  
4 the claims were being infringed, assuming they were  
10:33 5 valid, and not expressing an opinion as to whether or  
6 not the claims were valid or invalid?

7 A I really didn't -- I don't think I defined that  
8 for myself in any particular way. You could just read  
9 what I have to say, and I can answer questions about it  
10 that have to do with what I said. I didn't decide,  
11 "This is my response to this issue, and this is my  
12 response to this issue" when I was writing these things.  
10:34 13 I was just sort of looking at the whole thing, you know,  
14 from my point of view.

15 I mean, did you read the things that I wrote  
16 and do you have something specific in mind because I'll  
17 look at it and read it and see if that means something  
18 to me. It's not meaning much to me what you're saying.

19 Q I read your report and it looked to me to  
20 relate to the issue of infringement, and I have a whole  
21 bag of things to ask you if it relates to something  
22 other than infringement, and so the question is should I  
23 pull it out of my bag and ask you about it or should we  
10:34 24 talk about infringement?

25 MR. SWINTON: My objection is he was not --

1 it's clear in the report, the document speaks for  
2 itself, Dr. Mullis was asked to opine about the issue of  
3 infringement. I think you're trying to confuse things.

4 MR. LIPSEY: That's fine.

5 MR. SWINTON: Dr. Mullis --

6 MR. LIPSEY: That's fine, Counsel. I'm happy  
7 to take it from you. I just don't want to hear about it  
8 later that there was something else in there.

9 MR. SWINTON: Fine.

10 BY MR. LIPSEY:

11 Q Okay. Now, in preparing your report, did you  
12 review the prosecution history of the '338 patent?  
10:35

13 A I think in -- I mean, the prosecution history  
14 would include those documents like, say, Persing's  
15 declarations or whatever, Falkinham's comments. Is that  
16 what you mean by the prosecution?

17 Q Let's go back and lay a little foundation.  
18 You've filed patent applications and secured patents,  
10:35 19 correct?

20 A Yes.

21 Q And you understood the way you get a patent is  
22 by filing an application and there proceeds a give and  
23 take with the patent office where letters are exchanged  
24 back and forth and ultimately the patent issues, right?

25 A I usually don't do that. Lawyers do that. I

1 work with them.

2 Q But you're aware that that process occurs?

3 A That happens, yeah.

4 Q Did you review any of the materials of that  
5 process, the give and take with the patent office, in  
6 getting the '338 patent?

7 A I don't think I saw anything there that was  
8 like between a lawyer and the patent office. I may  
10:36 9 have. I may have forgotten that, but I don't think so.  
10 I think mainly I heard -- I read about other people's,  
11 you know, like I'm talking about other expert witnesses  
12 or whatever.

13 Q Okay. But --

14 A I don't remember seeing documents like directed  
15 to the patent examiner by a lawyer, but that doesn't  
16 mean I didn't see them. I just don't recall any.

17 Q Okay, fair enough.

18 Now, again, just trying to establish the  
10:36 19 playing field that we're on here, is it your belief that  
20 you have expressed in your report all of the bases upon  
21 which you base the opinions that are expressed?

22 A All of the bases under which I expressed --  
23 sometimes I just expressed my opinion without saying  
24 where it came from, I think. I mean, I'm not trying to  
10:37 25 be contrary here, but I don't understand what you're



1 asking me.

2 Q I mean, as I read your report, you state a  
3 series of opinions --

4 A Yes.

5 Q -- that bear on this issue of what is covered  
6 and what is not covered in the patent, and then you give  
7 a textural explanation for why that is your opinion. Is  
8 that a fair characterization of the structure of your  
9 report?

10 A I guess that's a fair characterization.

10:37 11 Q What I'm trying to find out is in the  
12 discussion portion of your report, have you stated all  
13 of the bases that you intend to rely upon to support the  
14 conclusions that you've given in the report?

15 A I would say no, because, I mean, my -- it's  
16 hard to like compartmentalize all of the information  
17 that I might bring to bear on the decision, you know, or  
10:38 18 an opinion in this thing, because it's my whole  
19 professional lifetime of experience that really -- I  
20 didn't describe every single thing that I happened to  
21 know or that, you know, that I would use in my -- in --  
22 I don't think that way. I don't say, "Because of this  
23 and this and this, these are all of the things that I  
24 know in that, I think this."

25 Sometimes with an issue as large as, like, the

1 specificity of various amplification techniques, I'm  
2 drawing on a lot of experience that I haven't really got  
3 the piece of paper -- a piece of paper in hand that I  
4 can say, "Here is why I know that." But I can talk  
5 about it at length if somebody wants to ask me why I  
6 have a particular opinion, and I can think through a lot  
7 of reasons that I have that particular opinion. I don't  
8 make up opinions, but I don't base them on specific  
9 little pieces of information all the time either.

10 I don't exclude that, but you're asking a  
11 question, is that all that I have drawn on to make these  
12 conclusions? I'm not in a position to tell you  
10:39 13 everything that I have drawn on. Not that I haven't  
14 drawn on something, but I just don't remember exactly  
15 where I learned each little thing that I know about this  
16 field.

17 If you can be really specific, I'd make a  
18 better answer to that question. If you say, "Where did  
19 you get your ideas for this particular statement that  
20 you made? Where did that come from?" then I can talk  
21 about it at length.

22 Q Sitting here today, are there reasons why you  
10:39 23 expressed the opinions you expressed in this report that  
24 you considered at the time and did not include in the  
25 report?

1           A    No.  Okay, I sort of understand what you're  
2 saying.  Not consciously, I did not leave something out  
3 that I really thought was pertinent.  I spoke freely and  
4 of my opinions and why I have them and so forth.  I  
5 wasn't covering anything or hiding anything or trying to  
10:40 6   dodge any issues.

7           Q    When did you first have occasion to read the  
8 Collins `338 patent which is the subject of your  
9 report?

10          A    I think that was one of the first documents  
11 that I was sent, and I really -- like I said, I'm not  
12 sure when that happened, but I bet it was a year ago at  
13 least.

14          Q    But to your knowledge that was the first time  
15 the Collins patent had come to your attention?

16          A    It wasn't a big shocking patent.  It didn't  
17 suddenly -- no, I would not have read it except for this  
10:40 18 case.

19          Q    Now, in your experience, professional  
20 experience reflected in your CV, was there ever a time  
21 when you were involved in the development of diagnostic  
22 assays?

23          A    Yes.

24          Q    Can you briefly describe when and where that  
25 was and what the general nature of the activity was.

1           A    Well, I think from the very beginning,  
7:41 2    developing PCR itself was -- you know, we started  
3    working with the first -- I mean, the first subject  
4    matter for use of PCR in anything more than just like  
5    model systems was analyzing for sickle cell anemia trait  
6    in DNA sample from a human. I mean, starting human  
7    blood and working to the DNA and doing the  
8    amplifications, that was a diagnostic test. That was  
10:41 9   the whole intention of the thing.

10           Q    That was in connection with your work at Cetus?

11           A    Cetus and then continuing at like a place  
12    called Xytronyx down in San Diego, I worked on a test  
13    there for Pneumocystis carinii, the organism. I've  
14    worked on various amplification systems relating to  
15    human DNA sequences where there are polymorphisms in the  
10:42 16   population.

17                   I've done that -- I've done that in, let's see,  
18    Burstein Technologies, I've worked on that problem. In  
19    my various consulting capacities to lots and lots of  
20    companies, that's very often the subject matter of what  
21    I'm consulting for is usually a company with a -- like a  
10:42 22    diagnostic test that they're trying to do or a procedure  
23    that they're working out to do lots of them.

24           Q    Were any of the diagnostic tests that you  
25    worked on actually commercialized?

1           A    PCR has been actually commercialized.  You  
2 might look in a copy of Science Magazine or something,  
3 yes.

4           Q    I mean in the context of the diagnostic test.

5           A    Yes, like the very first application, using for  
10:43 6 sickle cell anemia was commercialized.  And then a whole  
7 bunch of things.  Like, I mean, I worked on the HIV  
8 testing like for the actual nucleic acid of HIV in blood  
9 for Speciality Laboratories in Santa Monica where I  
10 was -- I mean, I worked there about three days a month  
11 for a couple of years and helped work out the techniques  
12 there.

13                   I also developed a method there for like  
14 rapidly purifying DNA out of a blood sample that could  
15 be used in -- in what was used in a lot of diagnostic  
16 tests.

17           Q    In any of that experience relating to  
18 diagnostic tests, have you had experience in developing  
10:44 19 non-specific amplification techniques?

20           A    No.

21           Q    Lest I have asked the question too narrowly,  
22 in your professional work reflected in your CV, whether  
23 or not directed to diagnostic applications, have you had  
24 experience with non-specific amplification techniques?

25                   MR. SWINTON:  Vague as to "experience."

10:44

1

THE WITNESS: No. My experience in the

2

diagnostic area originated with PCR, and I kind of never

3

looked back at that point. I've never gotten involved

4

in non-specific amplification techniques.

5

BY MR. LIPSEY:

6

Q Do you know any people who have?

7

A No. Do you? I can't find any. Actually, I

10:45

8

think I searched for that, just such a thing, and I

9

can't find anybody that is doing that commercially.

10

Q Okay. I'd like to ask you a couple of

11

questions about the development of PCR, and I know

12

you've been through this a thousand times, and I'll try

13

to keep it short.

14

I'd like the reporter to mark for

15

identification as Defendant's Deposition Exhibit 200 the

10:45

16

1985 Science publication by -- how do you pronounce the

17

name, Saiki, and others including Dr. Mullis.

18

(Defendant's Exhibit 200 was marked for

19

identification by the court reporter.)

20

BY MR. LIPSEY:

21

Q Is Defendant's Deposition Exhibit 200 the first

10:46

22

publication describing PCR?

23

A You know what, that's what I said. There

24

actually somewhere is an abstract that was published

25

earlier, just a brief abstract of the human genetics

45

1 meeting in Salt Lake City, which, I guess, really  
2 constitutes the first publication. It didn't describe  
10:46 3 details of how you would do it, and it wasn't like a  
4 formal paper that was reviewed or something, just like a  
5 couple of paragraphs that said "We've done this thing."

6 Q Okay. What was the date of that, if you  
7 recall?

8 A I think that is September 1985. I don't  
9 think -- it's not listed in my CV because it's not  
10 really a paper. It's just an abstract.

11 Q To your knowledge, Defendant's Exhibit 200 is  
12 the first formal paper describing PCR?

10:47 13 A Right.

14 MR. SWINTON: Let me just assert an objection  
15 for the record, that there are some interlineations on  
16 Exhibit 200. Just so the record is clear, those, I  
17 assume -- you're not representing they were part of the  
18 original publication? They came in some process other  
19 than Dr. Mullis?

20 MR. LIPSEY: Obviously, if they've been marked  
21 in some way, I'm not suggesting that's the way it  
22 appeared in Science.

23 Q Now, how long before the appearance of this  
10:47 24 publication had you invented PCR?

25 A I consider the invention to have happened, you

1 know, before I ever got it to work, and that happened in  
2 about May or early June of 1983, the first time that I  
3 actually got it to work. So like I say, this is not  
4 only in my mind, but it actually was December of 19-  
5 December 16th, 1983. That's when I showed it to a  
10:48 6 patent attorney and said "Look at this."

7 Q And is it correct that you have been involved  
8 in working with PCR first with Cetus and then with  
9 others essentially continuously since December of 1983?

10 A Sounds kind of boring, yeah. I've done a lot  
11 of other things, but I've been constantly called on for,  
10:48 12 you know, advice in projects, and I've done a few of  
13 them myself.

14 Q I apologize for some of these questions, but as  
15 I'm sure you've run into with other lawyers, we are not  
16 as technically trained as you are, and things that are  
17 clear to you sometimes are not clear to us.

18 In looking through this paper, it appeared to  
10:49 19 me that the experiment had been done with a 1-microgram  
20 sample of genomic DNA. Was that right? And  
21 specifically I'm looking at the legend in Figure 2.

22 A Yeah, at that point that's what we were using.

23 Q How was that -- I didn't see in the paper any  
24 description of how that was prepared. Do you recall how  
25 that was prepared?



1           A    I think at this point when this paper was  
2 published, that was prepared by -- in a large quantity,  
10:49- 3 you know, from like a lot of -- probably from a human  
4 blood sample, something like that. It was not prepared  
5 by me. It was something at this point in my association  
6 with diagnostics, it was a tube in a refrigerator that  
7 somebody else had put there and said, "This contains  
8 1/10 of a Microgram per milliliter of human DNA,"  
9 something like that.

10                   And we had several different -- we had some  
11 from cell cultures of human -- because there were a  
12 number of cell lines, one of which I can almost remember  
10:50 13 the number of it, GM 2064 something that did not have  
14 the hemoglobin sequences, didn't have beta globin in it.

15                   We had that. We had a line that had -- that  
16 was homozygous for sickle cell trait -- it's coming  
17 back -- SC-1, that's what that was called. And there  
18 was a wild type that had -- that was a heterozygote. So  
19 that would have been not purified from blood. The DNA  
10:50 20 would have been purified from human cell cultures that  
21 people had grown large quantities of.

22           Q    Well, whether it's from blood or cell cultures,  
23 how do you get the genomic DNA?

24           A    There is many ways to do that. You know, at  
25 that point the technology that we would have used to

1 purify the DNA for this paper would probably have been a  
2 chloroform phenol kind of extraction, where you mix the  
10:51 3 cells with -- actually, back then, probably somebody  
4 would have broken open the cells in some kind of little  
5 grinding device first, and then that would have been  
6 extracted with chloroform phenol to remove proteins and  
7 lipids, and then the DNA would have been probably  
8 precipitated from the aqueous solution there with  
9 ethanol. I think that would have been the procedure  
10 back then.

11 We would have wanted -- in the work we were  
10:51 12 doing for this, we would have been started -- before we  
13 would have started the amplification process, we would  
14 have managed to make purified human DNA that had very  
15 little of anything else in it but DNA.

16 Q Okay.

17 A We had lots of time. We weren't doing -- we  
18 weren't setting up a diagnostic routine there. We were  
19 developing the back end of one, but the front part we  
20 weren't really working on at that point.

21 Q When you say purified DNA, it had all of the  
10:52 22 DNA, including the stuff you were looking for and the  
23 stuff you weren't looking for, but it had been purified  
24 so that it didn't have stuff other than DNA?

25 A Right. It wouldn't have had proteins. It

1 probably -- and I'm not certain in that particular of  
2 the samples, I think it didn't have RNA in them either.  
3 I think they had been destroyed by enzymes, but it was  
4 whole human DNA.

5 Q Okay. I'm sorry for that digression.

10:52

6 Now, how quickly did PCR catch on as an  
7 amplification technique after its publication around  
8 Christmas of 1985?

10:53

9 A I think by June there would have been about  
10 seven or eight other papers that other people had  
11 published by then. By the next December, there were  
12 probably 150 to 200, and then up in the thousands by the  
13 next year, I think, and that's just my recollection. I  
14 may be foreshortening that a little bit because of my  
15 advanced age, but I think within about two years there  
16 were probably at least a thousand papers published using  
17 that for various things.

18 Q So I gather it caught on pretty quickly?

10:53

19 A It caught on pretty quickly, yeah. Especially  
20 after June, June is when I presented it to the Cold  
21 Spring Harbor Symposium, and that was like a whole lot  
22 of molecular biologists that had plenty of things they  
23 could do with it.

24 Q That was June of '86?

25 A June of '86.

1 Q Do you agree that by December of 1987, PCR was  
2 the most commonly used in vitro amplification technique  
10:54 3 known in the art?

4 A Yes.

5 Q Now, is it correct that even as late at 1987,  
6 you didn't recognize the applicability of PCR to  
10:54 7 techniques where the target DNA had already been  
8 isolated in pure form?

9 A Didn't -- wait a minute, I thought I just -- I  
10 did -- it was applicable to things where the target DNA  
11 had been isolated. Will you repeat that question. It  
12 seems like you got it backwards or I did.

13 Q Well, let me get at it this way. I'd like the  
14 reporter to mark for identification as Defendant's  
10:55 15 Deposition Exhibit 201 a copy of what appears to be a  
16 chapter out of Volume 155 Methods In Enzymology,  
17 entitled "Specific Synthesis of DNA in Vitro via a  
18 Polymerase-Catalyzed Chain Reaction," by Drs. Mullis and  
19 Faloona.

20 (Defendant's Exhibit 201 was marked for  
21 identification by the court reporter.)

22 THE WITNESS: That publication, by the way,  
10:55 23 was very slow coming out. That paper was completed  
24 probably a year before that hit the stands in a sense.  
25 That was a volume of a like a compendium kind of thing,

1 Methods In Enzymology. It doesn't come out monthly or  
2 anything like that. So the paper that -- that actually  
3 is a reworking of a paper that I submitted to Science  
4 and Nature, both of which publications rejected that  
5 paper, which was my original publication on PCR that  
10:56 6 later got published in Methods In Enzymology.

7 But it's not fair to say that that represents  
8 the state of the PCR technology in -- in the year or the  
9 month that that came out. It had -- that paper had sat  
10 around for a little while. Do you see what I mean?  
11 There were a lot of other papers out about PCR by that  
12 time, although that one was intended to be by me, the  
13 first one. It didn't work out that way.

14 MR. LIPSEY: Let's let the reporter mark it as  
10:56 15 Defendant's Exhibit 201.

16 Q In the first paragraph of Exhibit 201, starting  
17 at the end of the sixth line you state, "It is not  
18 necessary that the sequence to be synthesized  
19 enzymatically be present initially in a pure form; it  
20 can be a minor fraction of a complex mixture, such as a  
10:57 21 segment of a single-copy gene in whole human DNA." Do  
22 you see that?

23 A I remember writing it.

24 Q So at least at the time you wrote this,  
25 whenever that was, you didn't recognize the desirability

1 of using PCR in situations where the target nucleic acid  
2 was available in pure form, right?

3 MR. SWINTON: Argumentative.

4 THE WITNESS: The first reaction I ever did was  
5 on a nucleic acid in pure form. I may not -- the  
10:57 6 question is I didn't recognize the ability of PCR to  
7 amplify something that was already in pure form?

8 BY MR. LIPSEY:

9 Q Right.

10 A I certainly -- the experiments are in here.  
11 This experiment right here was done on a purified  
12 plasma. See that picture? I mean, the very first PCR  
13 reaction I ever did was on a purified plasma DNA. It  
14 wasn't on a human sample or anything like that.

15 Q So why --

16 MR. SWINTON: The written record ought to  
17 reflect that Dr. Mullis showed counsel the figure on  
10:58 18 page 337 of Exhibit 201.

19 BY MR. LIPSEY:

20 Q If you appreciated that, why did you make the  
21 statement that I read here, that it's is not necessary  
22 that the sequence to be synthesized enzymatically be  
23 present initially in pure form?

24 A Because it's not. You can start with a sample  
25 that is vastly impure, and I think in this paper I

1 showed that. Whole human DNA, you can use that, or you  
7:58 2 can use what I did in this experiment, a tiny little  
3 plasma that was completely pure. You can do it on  
4 either one.

5 If you're working out the details of how to set  
6 up a PCR reaction for the first time, which I was, in  
7 some of the experiments in here, of course I would start  
8 with a purified sample of DNA, a model system, and then  
9 I would try to see if that would work in a system where  
10 the DNA wasn't pure, like in a real system that you  
11 might have to work on in a real diagnostic experiment.

10:59 12 To say that it can be, it says it is not  
13 necessary that the sequence to be synthesized  
14 enzymatically be present initially in a pure form. It's  
15 not. It doesn't mean you can't start with something in  
16 a pure form. In fact, you can start with something that  
17 has been amplified already, and it's just one fragment.

18 Q So the ability to start with DNA that was not  
10:59 19 in pure form was a benefit of PCR but not a limitation  
20 on the application of its use?

21 A Right.

22 Q Okay. Sorry about that.

23 Now, the PCR amplification process that you  
24 invented or with respect to the PCR amplification  
11:00 25 process that you invented, all of the elements for its

1 implementation were available in the literature for  
2 years before you made the invention; is that right?

3 A For some little time, yes.

4 Q For 15 years, as a matter of fact?

5 A 15 years, it's -- yes, I think it's possible  
6 that the -- there -- you know, let's see from 15 years  
11:00 7 from 1983, that goes back to -- I'm not -- I think there  
8 was -- yeah, there were a few people in the world who  
9 had things like oligonucleotides, and there was a little  
10 bit of sequence known about natural DNAs, so there  
11 was -- it would have been possible.

12 It was a lot easier by, you know -- it would  
13 come -- after oligonucleotides became readily available  
1:01 14 in purified form and more and more sequences were being  
15 known, it made it a lot easier, but I think somebody --  
16 you're talking about 1970, though. I don't -- 15 years.

17 Q Let's try to help you out a little bit. I  
18 don't want to quibble with you. Let me mark for  
19 identification as Defendant's Deposition Exhibit 202 a  
20 copy of an article by Dr. Mullis appearing in Scientific  
21 American in April of 1990.

11:01 22 (Defendant's Exhibit 202 was marked for  
23 identification by the court reporter.)

24 BY MR. LIPSEY:

25 Q Exhibit 202 is an article you wrote, right?



1 A Yes.

2 Q And in the middle column at the end of the  
3 first complete paragraph, you point out that PCR lay  
4 unrecognized for more than 15 years after all the  
5 elements of its implementation were available, do you  
11:02 6 see that?

7 A Yes.

8 Q I gather you believed that to be correct at the  
9 time?

10 A I -- right. It could have been 14, could have  
11 been 15.

12 Q It was about that time?

13 A Right.

14 Q But notwithstanding that, you still got a  
15 patent on PCR, right?

16 A Well, having the elements available does not  
17 prevent someone from getting a patent on something. You  
18 can put the elements together in a novel way.

19 Q I'd like the reporter to mark for  
20 identification as Defendant's Deposition Exhibit 203 a  
21 copy of U.S. Patent No. 4,683,202.

11:02 22 (Defendant's Exhibit 203 was marked for  
23 identification by the court reporter.)

24 BY MR. LIPSEY:

25 Q Now, Exhibit 203 is one of the patents listed

1 on your CV that I think you said you reviewed in  
2 preparing your expert report?

3 A Yes.

4 Q Okay. And is it fair to characterize Exhibit  
11:03 5 203 as the basic patent on the PCR process?

6 A Yes.

7 Q And I think you said in your expert report that  
8 PCR is a specific amplification technique; is that  
9 right?

10 A Yes.

11 Q And I think you also said it is an exponential  
12 amplification technique; is that right?

13 A Yes.

14 Q Would you turn to column 27 of the Exhibit 203,  
11:03 15 please.

16 Do you see there claim 1, and that -- can you  
11:04 17 tell me, after you've done the steps that are outlined  
18 there in claim 1, how many copies of the target  
19 polynucleotide do you have? You can take a moment to  
20 read it.

21 A You assuming you start with one?

22 Q Yes, assuming you start with one.

23 A I think these steps --

24 Q Why don't you take a moment and just read it to  
25 yourself.

1           A    You go from one to four.  It's taking you  
11:04 2           through -- it's starting with whatever this target was,  
3           it's making two -- making that into two things and then  
4           taking those things and making them into four things.

11:05 5           Q    So at the end of the steps here in claim 1, you  
6           would have four copies of the target, is that right,  
7           assuming you started with one?

8           MR. SWINTON:  Objection; legal conclusion.

9           THE WITNESS:  I -- yes, that's the way I would  
10          describe it.

11         BY MR. LIPSEY:

12          Q    And in claim 2, it says that one of the  
13          possibilities is to repeat steps B and C once; do you  
14          see that?

15          A    Yes.

16          MR. SWINTON:  Objection; misstates.  It says at  
17          least once.

18         BY MR. LIPSEY:

19          Q    If you repeated steps B and C once, how many  
11:05 20          copies of the DNA would you have at that point?

21          A    Every time you repeat it, you double the number  
22          of copies, so you would probably -- if you did it one  
23          time, then you would get eight, so at least eight.

24          Q    Okay.  That's fine.

25          Now, one of the enzymes you contemplated for

1 use in the PCR process was the Klenow fragment of E.coli  
1:06 2 DNA polymerase 1; is that right?

3 A Yes.

4 Q And, in fact, that's one of the ones mentioned  
5 in claim 7; is that right?

6 A Yes, it is.

7 Q Now, when you used the Klenow fragment to do  
8 PCR, you can get some non-specific amplification; is  
11:06 9 that right?

10 A You can -- yes, you will get some  
11 non-specific. You don't intend to, but that's the way  
12 the universe works, particularly biochemical reaction.

13 Q I'd like the reporter to mark for  
14 identification as Defendant's Deposition Exhibit 204 a  
15 copy of an article appearing in Science in January of  
11:07 16 1988, authored by Dr. Saiki and Mullis and others.

17 (Defendant's Exhibit 204 was marked for  
18 identification by the court reporter.)

19 BY MR. LIPSEY:

20 Q Exhibit 204 is an article you co-authored; is  
11:07 21 that right?

22 A Yes.

23 Q This appeared in Science in January of 1988,  
24 down in the lower left-hand corner?

25 A Right, yes.

1 Q Would you turn to the second page of the  
2 exhibit, please., In the left-hand column, starting  
3 seven lines down, it states, "Electrophoretic  
11:08 4 examination of the reactions catalyzed by the Klenow  
5 polymerase reveals a broad molecular size distribution  
6 of amplification products that is presumably the result  
7 of non-specific annealing and extension of primers to  
8 unrelated genomic sequences under what are essentially  
9 nonstringent hybridization conditions. Klenow  
10 polymerase reaction buffer at 37 degrees C." Do you see  
11:08 11 where I've read?

12 A Yes.

13 Q Okay. Is that the phenomenon of unintended  
14 non-specific amplification with Klenow fragment that you  
15 just mentioned?

16 A Whether it's intended or not, I mean, is hard.  
17 I mean, I knew it was going to be that way. We all knew  
18 it was going to happen, but it wasn't what we really  
19 wanted, which is what happens when you gets a hot  
20 mixture, you get a lot better specificity.

21 Q To use the hot mixture, you have to use a  
11:09 22 thermostable polymerase like Taq; is that right?

23 A Right.

24 Q Now, even with PCR, you get linear  
25 amplification of the original long fragment of target

11:09 1 DNA; is that right?

2 A The long fragments accumulate in a linear  
3 fashion because they're the product of the original  
4 template in the primers, so that's the same in every  
5 cycle.

6 Q Are there commercial products of which you're  
7 aware that employ linear amplification?

11:10 8 A I -- I don't think so, but I, you know, I may  
9 be failing to remember some particular product, but I  
10 know that it's -- it works a lot better if you have an  
11 exponential reaction. I can't think of anybody who has  
12 a product that -- you know, there is a lot of modern  
13 little techniques that just might have that involved. I  
14 know when you're trying to sequence DNA, at some point  
15 you want to inhibit the exponential reaction because you  
16 try to produce a lot of single stranded DNA to sequence,  
17 and in that part of the reaction, it becomes linear.

18 By then you've amplified up from a, you know,  
19 a -- you've usually amplified in an exponential process  
20 first, and then you take a little bit of that and start  
11:11 21 this process that only has one primer in it to generate  
22 single strands and you are making more. There may be  
23 even by now commercially available kits for doing just  
24 that and not amplifying prior to that because the  
25 sensitivity of detection has gotten so high that it's

1 not -- if you start with something that is fairly  
2 abundant anyhow, you maybe don't even have to do  
3 exponential amplification, but I'm not currently up with  
11:11 4 the very latest techniques in those big sequencing  
5 companies, so I'm not really certain whether they ever  
6 start from an unamplified sequence. They may. There is  
7 no theoretical reason why you couldn't.

8 Q So, I gather the difference between a linear  
9 specific amplification technique and exponential  
10 specific amplification technique is that in a linear  
11:12 11 technique, you would use a single specific primer  
12 whereas in the exponential technique, you need to use  
13 two or more; is that correct?

14 A I -- yeah, I think that's fair to say. If  
15 you -- you could make copies of a single strand with  
16 just one primer and every cycle you would get another  
17 copy, that would be linear.

18 Q Okay. Now, the basic techniques needed to do  
11:12 19 the individual steps of PCR were generally known in the  
20 art even at the time you filed your application for the  
21 patent, which we have here as Defendant's Exhibit 203;  
22 is that correct?

23 A Yes, in a general way. The actual specific  
11:13 24 times and temperatures and stuff that I used may not  
25 have been published somewhere, but the idea of -- in

1 fact, the reason we were making oligonucleotides in the  
2 first place was to bind them to single strands of DNA  
3 and extend them once, or either bind them and just  
4 define that strand on the gel or something. Those  
5 techniques were already -- there were several recipes  
6 available for extending an oligonucleotide on a  
11:13 7 template.

8 BY MR. LIPSEY:

9 Q But techniques for making oligonucleotide  
10 primers were known in the art even at the time of your  
11 patent application?

12 A Oh, sure.

13 Q And techniques for separating the strands of  
14 double stranded DNA were known at that time too?

11:14 15 A Yes.

16 Q And techniques for second strand synthesis  
17 starting with the primer were known at that time?

18 A Yes, techniques for extending a primer on a  
19 template were known.

20 Q Now, in your patent, Defendant's Exhibit 203,  
11:14 21 you have a discussion of the use of PCR for detection  
22 techniques; is that correct?

23 A I think so, yeah.

24 Q Okay. And I can point you to it if you'd  
25 like. That discussion extends from about column 13,



1 line 4 3 over to column 15, line 37 or so. Do you see  
2 that?

1:15

3 A Okay.

4 Q Okay. Now, in that discussion of detection  
5 techniques using PCR, you did not describe the  
6 combination in a detection assay of target capture with  
11:15 7 amplification by PCR; is that right?

8 MR. SWINTON: Vague as to "target capture,"  
9 best evidence.

10 THE WITNESS: In this discussion, I don't think  
11 I said anything about target capture.

12 BY MR. LIPSEY:

13 Q Okay. And indeed in the examples of your  
14 patent, you didn't say anything about the combination of  
15 target capture of PCR either, right?

16 A I don't think in any of those examples I was  
11:16 17 dealing with that issue at all.

18 Q And you expected that the claims of your patent  
19 wouldn't be limited just to the specific embodiments  
20 that you described in the text, right?

21 MR. SWINTON: Objection; legal conclusion,  
22 relevance, beyond the scope of his opinions.

23 THE WITNESS: My answer to that was, certainly  
24 I did think it was going to go beyond the scope of just  
25 the exact claims -- not the claims, but the examples

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that I made.

BY MR. LIPSEY:

Q Indeed you said that in column 27 of your patent at about line 25, do you see that?

MR. SWINTON: Same objections.

THE WITNESS: I think it's customary to say something like that, yeah.

BY MR. LIPSEY:

Q Do you believe that your patent covers the use of PCR in diagnostic assays when combined with a preliminary target capture technique?

MR. SWINTON: Objection; legal conclusion, beyond of scope of his opinion, incomplete hypothetical.

THE WITNESS: I think it applies any time you use PCR under any circumstances. Doesn't matter what you've done before or what you do later.

MR. LIPSEY: Why don't we take a short break and get organized.

THE VIDEOGRAPHER: This is the end of tape number one of Volume 1. We're off the record at 11:17.

(Recess.)

THE VIDEOGRAPHER: This is the beginning of tape number 2, Volume 1. We're on the record at 11:25.

MR. LIPSEY: I'd like the reporter to mark for identification as Defendant's Deposition Exhibit 205 a

1 copy of U.S. Patent 4,683,195 naming Dr. Mullis as a  
2 coinventor.

3 (Defendant's Exhibit 205 was marked for  
4 identification by the court reporter.)

5 BY MR. LIPSEY:

6 Q Dr. Mullis, Exhibit 205 is another one of your  
7 patents relating to PCR; is that right?

8 A Yes.

11:26 9 Q This is one of the patents you identified as  
10 having been reviewed in the course of preparing your  
11 expert report; is that right?

12 A Reviewed, but not memorized.

13 Q Fair enough.

14 In this patent, Exhibit 205, the claims are  
15 directed to processes for detecting the presence or  
11:26 16 absence of specific nucleic acid sequences in a sample  
17 using PCR, correct?

18 MR. SWINTON: Objection; legal conclusion, best  
19 evidence.

20 THE WITNESS: Would you repeat exactly what you  
21 said, detecting -- doing PCR for purposes of detecting,  
22 cloning, whatever else I think we've said.

23 BY MR. LIPSEY:

24 Q Well, if you take a look at column 40, you'll  
25 see Claim 1 is there, and basically whereas your other

66

11:27 1 patent, Exhibit 203, claimed basically the process of  
2 amplification using PCR, this patent, Exhibit 205,  
3 claims processes for detecting the presence or absence  
4 of at least one specific nucleic acid in a sample using  
11:27 5 PCR.

6 A Right.

7 MR. SWINTON: Same objections.

8 BY MR. LIPSEY:

9 Q Now, we spoke a moment ago about the fact that  
10 there is some non-specific amplification, even with PCR,  
11 and that is true with respect to the TMA process as  
12 well; is that right?

11:28 13 A Yes.

14 Q I'd like the reporter to mark for  
15 identification as Defendant's deposition Exhibit 206 the  
16 text of an article appearing in McGraw-Hill's  
17 Biotechnology Newswatch October 6, 1986, entitled "DNA  
11:28 18 cleavage adapter groomed for genetic diagnostics."

19 (Defendant's Exhibit 206 was marked for  
20 identification by the court reporter.)

21 BY MR. LIPSEY:

22 Q Do you recall seeing Exhibit 206 before?

23 A It's not altogether novel, but let me just  
11:29 24 understand what this is. Okay.

11:29 25 Q The second-to-last paragraph of the article

1 attributes some quotes to you. Well, I guess let me get  
2 an answer. Have you seen Exhibit 206 before?

3 A I -- it seems familiar, but it's probably a  
4 long time ago.

5 Q Would you take a look at the penultimate  
6 paragraph on the second page where there are some quotes  
7 attributed to you. Do you see that?

11:30

8 A Yes.

9 Q Okay. The Mullis technique referred to there  
10 is a reference to PCR, is that your understanding?

11 A Yes.

12 Q And then you're quoted as saying "You do get a  
13 lot of other things replicating that you don't want, but  
14 the background is low enough to be readable." Do you  
15 see that?

16 A Yes.

17 Q Is it your belief that that's a correct  
18 quotation from you?

19 A Yes.

11:30

20 Q Okay. I'd like the reporter to mark for  
21 identification as Defendant's Deposition Exhibit 207 a  
22 copy of an article appearing in the Cold Spring Harbor  
23 Symposium on Quantitative Biology from 1996 entitled  
24 "Specific Enzymatic Amplification of DNA In Vitro: The  
11:31 25 Polymerase Chain Reaction."

1 (Defendant's Exhibit 207 was marked for  
2 identification by the court reporter.)

3 BY MR. LIPSEY:

4 Q Exhibit 207 is another publication co-authored  
5 by you; is that right?

6 A Yeah.

7 Q Would you turn to page 272, please.

8 A Okay.

11:31 9 Q In the left-hand column at the end of that  
10 first incomplete paragraph, the statement is made, "As a  
11 further simplification, PCR amplification has been  
12 performed directly on crude cell lysates, eliminating  
13 the need for DNA purification." Do you see that?

14 A Yes.

15 Q Is that a benefit of PCR or a limitation on its  
16 use?

17 A That's the benefit of it. You can do that.

18 Q Now, working backward through the paper, if you  
19 turn back to page 270 -- and the actual discussion  
11:32 20 starts on 269, and feel free to look back at that at the  
21 context -- but there in the first complete paragraph on  
22 page 270, there is an indication that -- of cloned DNA  
23 sequences that had been amplified by PCR, only about 1  
24 percent of them had the DNA fragment of interest; is  
25 that correct?

11:33 1 A It says only about 1 percent of the clones  
2 hybridized to the internal beta globin probe. Let me  
3 make sure I understand what is happening here. Right, I  
4 understand what it's saying. It is saying basically 99  
5 percent of the sequences that were amplified out of that  
6 were not exactly -- were not beta globin.

7 Q Okay. And you indicate here that those other  
11:33 8 sequences were presumably amplifications of other  
9 segments of the genome rather than the one you wanted;  
10 is that right?

11 A That's probably one of the worst cases there  
12 because the globin family is an enormous super family of  
13 many sequences that all have very similar but not  
14 exactly the same sequence, so it's a bad -- it's one of  
15 the worst. It just happens that is the one we first  
16 started working with, and it was an unusually -- we did  
11:34 17 better than 1 percent, but in that case, that was using  
18 Klenow and that was with that particular site.

19 Q Over in the right-hand column on page 270,  
20 there is another experiment described where 80 percent  
21 of the cloned fragments that had been amplified with PCR  
22 were not the correct fragment; is that right?

23 A Right.

11:34 24 Q And your statement at the time about the cause  
25 of that was, "At this time the basis for the difference

1 in the specificity of amplification defined here is the  
2 ratio of target to nontarget clones is not clear but may  
3 reflect the primer sequences and their genomic  
4 distribution." What does that mean?

11:35

5 A That means the sequences, like the beta globin,  
6 the target sequence for beta globin is one of a super  
7 family of similar genes, and those primer sequences that  
8 were intended, they only occur once in their actual  
9 sequence, but there are several variations of them in  
10 various other places around the genome.

1:35

11 So the sequences that we chose to amplify, that  
12 110 I think it was, were present in lots of different  
13 locations due to -- I mean, similar sequences to them  
14 were. So that's were the 1 percent -- I was trying to  
15 explain the difference between the beta globin case  
16 where you get 1 percent and the HLA-DQ alpha case where  
17 we got 20 percent.

18 And the HLA-DQ alpha is a very much more unique  
19 gene sequence than is the beta globin. So we were  
20 speculating at that point, and that's all we could do,  
21 but it looked -- it seemed reasonable that is what was  
22 going on.

11:36

23 Q So, one of -- the solution that you propose in  
24 this article for dealing with this amplification of  
25 something other than the target was to use nested sets



1 of PCR primers; is that right?

2 A Right.

3 Q Okay. And by that, you mean using four or  
4 perhaps even more primers instead of two in order for  
5 the PCR reaction to amplify only the target that you're  
11:36 6 interested in?

7 A Right. In effect, it's like you're doing two  
8 PCR reactions in a row. One of them you're doing on the  
9 whole human DNA, and then the other one you're doing on  
10 the product of that first one, which is now greatly --  
11 although there's only 1 percent of beta globin in there,  
12 that compares to like 100,000th of a percent that was in  
13 there in the beginning, so it's relatively enriched.

14 And then after another level of that with the  
15 second set of primers, it goes up to a pretty much  
16 homogeneous sample, as you can see on the gels there.

17 Q And earlier in the paper, back on page 265,  
11:37 18 down on the bottom of the left-hand column, you indicate  
19 down there that sometimes PCR produces a molecule  
20 exclusively representative of the intended target and  
21 sometimes it does not.

22 MR. SWINTON: I'm sorry, direct me where it is.

23 MR. LIPSEY: It's in the lower left-hand  
24 column, under the heading "Nested Primer Sets."

11:38 25 THE WITNESS: On page --

1 BY MR. LIPSEY:

2 Q 265.

3 A 265.

4 MR. SWINTON: I'm going to ask, somebody has  
5 got to reread that, either you read it or the court  
6 reporter..

7 MR. LIPSEY: I'll do it.

8 Q At page 265 of Defendant's Exhibit 207, in the  
9 lower left-hand corner, you indicate that sometimes PCR  
10 produces a molecule exclusively representative of the  
11 intended target and sometimes it does not; is that  
12 right?

13 A Yes.

14 Q And that's a reference to the phenomenon that  
11:38 15 we just talked about that was discussed over on page  
16 270; is that right?

17 A Right.

18 Q Okay. Now, in your expert report, you  
19 indicated that the problem with non-specific  
20 amplification was that it amplified all the other junk  
21 in the sample along with the target so that you never  
11:39 22 found the target. Is that a fair summary of one of your  
23 objections to non-specific amplification?

24 A Well, I don't remember using the word junk, and  
25 I don't remember the -- using the expression never found

73

1 the target. The target was not the only thing on the  
2 gel, and sometimes -- I mean, that's what some of the --  
3 this process of nested primers was directed to that as a  
4 problem and solved it.

11:39

5 Is there any doubt in anybody's mind that the  
6 PCR reaction does not necessarily simply amplify one  
7 single molecule exactly, that there are other molecules  
8 that are similar that also get amplified? I think  
9 that's what I'm saying right there, right?

10 Q I was actually moving on to a different topic.

11 A Okay, well, move on.

12:40

12 Q I'm sorry, maybe we ought to take a look at  
13 your expert report so that we don't get confused. If I  
14 can find your expert report. Your report is marked as  
15 Exhibit 198. Do you have it?

16 A I think I probably do. Yes.

11:41

17 Q Would you turn to page 8. There you point out  
18 one of the benefits of specific amplification, and PCR  
19 in particular, is the ability to find a needle in the  
20 haystack. Do you see that?

21 A Um-hum, yes.

11:41

22 Q And you indicate in contrast that non-specific  
23 amplification doesn't let you find the needle in the  
24 haystack because it amplifies something other than the  
25 target DNA.

1 A The whole haystack.

2 Q I'm sorry?

3 A It just makes a new haystack with its own  
4 needle in it. It doesn't really give you an edge on it.

5 Q But the possibility of non-specific  
6 amplification in a PCR process can also make it  
7 impossible to find the needle in the haystack; isn't  
8 that right?

9 A The word -- using this word as two kinds of  
10 things, specific and non-specific, and in a verbal  
11:42 11 sense, that's true. But in an actual chemical reaction,  
12 there is many degrees of specificity, and PCR is much  
13 more specific than methods that aren't even designed to  
14 be specific, obviously. It's not absolutely specific.  
15 Even if you started with just one molecule of some pure  
16 substance, you would probably get a couple of  
17 misprimings and some things that you weren't intending  
18 to get because that's the way stochastic kind of  
11:42 19 biochemical reactions happen to work.

20 It's very different than somebody just -- like  
21 a carpenter doesn't make that kind of mistake. He makes  
22 a chair, he makes a chair. He doesn't make five things  
23 that look kind of like chairs and one that does.

24 But that's the way biochemical reactions are.  
25 It may be a little confusing to say this is specific and

1 this is non-specific. Like everything to some degree is  
2 non-specific, but the level of that can vary over like a  
11:43 3 factor of a billion or 100 billion fold, so you have to  
4 be -- I mean, there are shades of meaning all the way  
5 out from just a little bit more than random to extremely  
6 specific, and the extremely specific amplification  
7 reactions is why people got all excited, not the ones  
8 that that were non-specific. No one got excited about  
9 that.

10 Q Okay. But even in the case of PCR, it's  
11 possible for a non-specific amplification event to  
11:43 12 prevent you from finding the needle in the haystack;  
13 isn't that right?

14 MR. SWINTON: Incomplete hypothetical, assumes  
15 facts.

16 THE WITNESS: I -- even on the worst of days, I  
17 was usually able to find something that looked like it  
18 could be a bunch of different needles. But yeah, they  
19 can vary all the way from being very non-specific to  
11:44 20 very specific, depending a lot on the target you're  
21 looking for in the first place, its initial frequency,  
22 the -- your choice of the primers, whether you got lucky  
23 and hit some very unique sequences, whether you're doing  
24 the reactions at a very high temperature and being  
25 careful with not having any primings happening at low

1 temperatures.

2           You get the whole range of possibilities. With  
3 PCR you do have the possibility on one end of basically  
4 ending up with a gel that looks like there is just one  
11:44 5 thing on it, and that is sort of the definite, sort of  
6 the thing that got people excited about PCR. If you  
7 look back at those gels in the early days when we didn't  
8 have Taq polymerase and we were doing them at room  
9 temperature, there was a lot of different things on a  
10 gel where you were hoping to get just one band, but you  
11 knew you were going to get a lot of stuff. But you  
12 still got a selective amplification of that one thing,  
13 like it maybe got purified by a factor of say a million.

14           Q But it is still possible with PCR, because of  
15 non-specific amplification events, to end up with a gel  
16 that has just one thing on it that isn't what you're  
17 looking for, right?

18           MR. SWINTON: Incomplete hypothetical.

19           THE WITNESS: I don't know whether I ever had  
20 that happen where it just has one thing on there that  
21 wasn't -- I don't see how you can get that to happen  
22 actually. Can you find an example of that somewhere  
23 where you got one band and it was the wrong one?

24           MR. LIPSEY: Funny you should mention that.

25           I'd like the reporter to mark for

11:45 1 identification as Defendant's Deposition Exhibit 208 an  
2 article published in 1990 by Dr. Mullis entitled "Target  
3 amplification for DNA analysis by the polymerase chain  
4 reaction."

11:46 5 (Defendant's Exhibit 208 was marked for  
6 identification by the court reporter.)

7 BY MR. LIPSEY:

8 Q Okay. Is Defendant's Exhibit 208 an article  
9 written by you?

10 A Yeah, I think this is probably, it was  
11 either -- yes.

11:46 12 Q What was the journal it appeared in?

13 A I'm trying to figure that out. It's got a --  
14 some French thing because it has an abstract here.  
15 First Congress on Advanced Concepts in Biology in Paris,  
16 I guess it's a journal that is published by -- or maybe  
17 like a symposium kind of volume.

18 Q There is some abbreviation in the lower  
19 right-hand corner of the first page. I'm just not  
20 familiar with it. Do you know what that is?

11:47 21 A First Conference of Advanced Biotechnology,  
22 Paris. I don't remember it exactly.

23 Q On the right-hand side of the page.

24 A Oh, Annals of Biologica Clinica, 1990, okay,  
25 right.

1 Q What journal is that again? I just wasn't  
2 familiar with the abbreviation.

3 A I'd say it's probably in French right, it's  
4 probably Annalia Biologica Clinica (phonetic), something  
5 like that, it's just abbreviated there. It doesn't have  
11:47 6 a name.

7 Q Now, would you turn to page 582, please. There  
8 in the paragraph bridging the two columns you talk about  
9 some of the problems that arise by doing PCR at lower  
10 temperatures. Do you see that?

11 A Right.

12 Q And you state "By doing so, you generate a  
11:48 13 large number of incorrect extension products with the  
14 promiscuous oligomer at one end. Some of them,  
15 especially the long ones, will provide a site for a  
16 second primer to bind, and then you can have a fragment  
17 which can be amplified. But it isn't the one your grant  
18 was written about." Do you see that?

19 A Yes.

20 Q When you say "it isn't the one your grant was  
21 written about," you mean it's not the DNA you were  
11:48 22 trying to amplify in connection with the research grant  
23 that --

24 A Right, in other words, I've said this in sort  
25 of tongue in cheek, but it is possible that there is an



1 amplification product there that is not the -- the  
2 sequence is not exactly what your sequence is, but there  
3 is maybe a lot of it there to start with, and so your  
4 sequence is kind of lost. It doesn't get amplified.  
5 But I'm not recommending that as you'll notice. I'm  
11:49 6 saying that's if you did it all wrong, if you're running  
7 the reaction and you let it sit on the bench at room  
8 temperature for a while, I wouldn't consider that to be  
9 an intrinsic limitation of PCR. It's one way that it  
10 can go wrong, and it's suggesting how to avoid that here  
11 in this paper. Not saying that's the way it usually  
12 happens.

13 Q You go on to say, "Enough of these voluntary  
14 fragments can choke a PCR reaction to death at the level  
15 of the finite supply of polymerase before the intended  
11:49 16 target has been amplified to the level required by your  
17 detection system."

18 A Certainly can. And this is -- I mean, like I'm  
19 saying, it's not an intrinsic limitation on the reaction  
20 itself, as there are solutions to that, but even if  
21 the -- if you're trying to amplify something that is  
22 like one part in like 40 quadrillion or something, which  
23 is sometimes -- that's not an imaginary number when  
11:50 24 you're looking for a single sequence of, say, HIV DNA  
25 sequence in the presence of like 5 milliliters of blood,

1 and all of the DNA from it, you -- I mean, there, you  
2 can get a lot of -- sometimes, I mean, if you do the  
3 reactions in the cold and you're looking for such a tiny  
4 thing, your product is going to get amplified by the  
5 other things in there, so many other things in there,  
6 they're going to get amplified to the point where they  
7 just sort of just drown it out.

8 I think if you read this carefully, you'll see  
11:50 9 we're talking about real extreme cases, where even in  
10 those extreme conditions, there are remedies for that.  
11 The reaction can be extremely specific, and it's  
12 intended to be specific. It's not intended to work like  
13 that. It's just sometimes if you really pile up a lot  
14 of things against you, make it as hard as possible just  
15 for the sake of doing that, you can make it almost  
16 impossible to see the target you're looking for. But in  
17 the context of the way you said that, like something  
18 comes up that is the wrong thing and that is the only  
11:51 19 thing you see, that's not -- that's not generally the  
20 case. That's like the extreme.

21 Q Okay. But it was an event that was  
22 sufficiently probable that you felt the need to counsel  
23 readers about it in this publication in 1989 or 1990; is  
24 that right?

25 A It was an event that I felt was not

1 necessarily -- it was necessary -- I mean, I wrote the  
2 paper about it. I spent a long time, in fact,  
11:51 3 developing techniques to avoid it, and then I reported  
4 those techniques here.

5 Q Okay. I'd like the reporter to mark for  
6 identification as Defendant's Deposition Exhibit 209 a  
7 publication by Dr. Mullis appearing -- published by the  
8 Cold Spring Harbor Laboratory Press in 1991 entitled,  
9 "The Polymerase Chain Reaction in an Anemic Mode: How  
11:52 10 to Avoid Cold Oligodeoxyribonuclear Fusion."

11 (Defendant's Exhibit 209 was marked for  
12 identification by the court reporter.)

13 MR. SWINTON: He always smiles when he gets the  
14 tough words right.

15 BY MR. LIPSEY:

16 Q Exhibit 209 is another article that you wrote;  
17 is that right?

18 A Yes.

19 Q And you make reference here to the problem when  
11:52 20 conducting PCR of getting I think what you called ugly  
21 little fragments, right?

22 A Yes.

23 Q And the ugly little fragments are the ones that  
24 arise from unintended priming events, right?

25 A Yes.

1 Q And you indicate that those ugly little  
2 fragments can be a particular problem -- or let me  
3 rephrase that.

4 You indicate that those unintended priming  
5 events can be a particular problem when you're looking  
6 for a needle in a haystack, right?

7 A Yes.

8 Q I'd like the reporter to mark for  
11:53 9 identification as Defendant's Deposition Exhibit 210 a  
10 copy of an article by Dr. Mullis and others with the  
11:54 11 first named author being Kwok, K-w-o-k, appearing in the  
12 Journal of Virology May 1987.

13 (Defendant's Exhibit 210 was marked for  
14 identification by the court reporter.)

15 BY MR. LIPSEY:

16 Q Exhibit 210 is an article co-authored by you;  
17 is that right?

18 A Yes.

19 Q And is this one of the articles you indicated  
11:54 20 that you looked at in the course of preparing your  
21 expert report?

22 A Yes.

23 Q And this article was published in 1987; is that  
24 right?

25 A Right.

1 Q And it relates to development of an assay for  
2 AIDS; is that right?

3 A Well, for the HIV virus. I don't think it was  
4 for AIDS.

5 Q And that assay employed PCR amplification; is  
6 that right?

7 A Yes.

11:55 8 Q Okay. But the assay described in this paper  
9 didn't combine the step of target capture prior to  
10 amplification; is that right?

11 MR. SWINTON: Vague as to "target capture."

12 THE WITNESS: As far as I remember, we weren't  
13 doing target capture.

14 BY MR. LIPSEY:

15 Q Okay.

11:55 16 A I think we were doing analytical work on the  
17 back end to try to see if we were looking at -- here  
18 again, we were looking at trying to find one tiny thing  
19 in the presence of a lot more than just like one gene in  
20 a human gene -- we were looking for a viral gene that  
21 could be there. Nobody wanted any of it in their blood,  
22 so if you take a 5-milliliter blood or a milliliter  
23 sample, you want to say there is not a single one in  
24 there. So this was pushing the technology, and it was  
25 pretty early in the -- it was 1987, so --

11:56

1

Q I'd like the reporter to mark for

2

identification as Defendant's Deposition Exhibit 2 --

3

strike that.

4

I'd like to show you a copy of a document that

5

has previously been marked for identification as

6

Plaintiff's Exhibit 5 in this action, which is the '338

11:56

7

patent.

8

Okay, now, I think you indicated in your expert

11:57

9

report you had read the text and claims of the patent;

10

is that right?

11

A Yes.

12

Q Okay. On the first page of Plaintiff's Exhibit

13

5, there is an abstract, do you see that?

14

A Yes.

15

Q Okay. It says "A method of assay for target

16

polynucleotides includes steps for isolating target

17

polynucleotides from extraneous non-target nucleotides,

11:57

18

debris and impurities and amplifying the target

19

polynucleotide." Do you see where I'm reading?

20

A Yes.

21

Q There is no reference to non-specific in that

22

sentence, is there?

23

MR. SWINTON: Best evidence.

24

THE WITNESS: It doesn't say anything at all

25

about the specificity of the amplification. That is an

85

1 abstract, however.

11:58 2 BY MR. LIPSEY:

3 Q Would you turn to column 2 of the '338 patent,  
4 Plaintiff's Exhibit 5. See there starting at about line  
5 9 there is a definition of the term amplify?

6 A Yes.

7 Q And there is no reference in that definition to  
8 non-specific amplification, correct?

9 A Let's see, I think the guy that wrote this had  
11:58 10 better vision.

11 Q Certainly the guy who printed it.

12 A Right. And the question you had was there is  
13 no reference to the specificity in that?

14 Q There is no reference to non-specific  
15 amplification in that definition in column 2, is there?

11:59 16 MR. SWINTON: Same objection.

17 THE WITNESS: I don't see any part of that that  
18 is directed to specificity. It doesn't say anything one  
19 way or the other. There is nothing in the first  
20 paragraph right after background of the invention about  
21 it either, but it doesn't really prove anything, does  
22 it?

23 BY MR. LIPSEY:

24 Q Would you turn to column 9, please. And there  
11:59 25 starting at about line 42 the text states "The invention

1 also features a method for assaying a sample for a  
2 target polynucleotide which sample contains the target  
3 polynucleotide and non-target polynucleotides. The  
4 method involving contacting the sample with a  
5 polynucleotide probe capable of forming a complex with  
6 the target polynucleotide, substantially separating the  
7 complex from the non-target nucleotides in the sample,  
12:00 8 amplifying the target polynucleotide, to form an  
9 amplification product and measuring or detecting the  
10 amplified target polynucleotide." Do you see where I've  
11 read?

12 A Yes.

13 Q There is no reference to non-specific  
14 amplification there either, is there?

15 MR. SWINTON: Same objection.

16 THE WITNESS: Notice, again, the author is  
17 not -- he has not gotten into that issue in any of those  
18 places. The answer is no, it doesn't say anything about  
12:00 19 it, as I'm sure you checked before you read it.

20 BY MR. LIPSEY:

21 Q Just wanted to make sure. Would you turn to  
22 column 15, please. Starting at about line 39 it states,  
23 "An embodiment of the present method can" -- should say  
24 be -- "practiced with additional amplification steps to  
25 generate an amplification product to improve the



12:01

1 sensitivity of the assay." Do you see where I've read?

2 A Yes.

3 Q There is no reference to specific  
4 amplification -- excuse me, there is no reference to  
5 non-specific amplification in that sentence, correct?

6 MR. SWINTON: Best evidence.

7 THE WITNESS: None.

8 BY MR. LIPSEY:

9 Q I'm sorry?

10 A I don't see any. I mean --

12:01

11 Q Okay. Turn to column 30, please. Starting at  
12 about line 15 the text states "The sensitivity of the  
13 above DNA or RNA target capture methods can be enhanced  
14 by amplifying the captured nucleic acids." Do you see  
15 where I've read?

16 A I see what you read, yes.

17 Q There is no reference in that sentence to  
18 non-specific amplification, correct?

19 MR. SWINTON: Same objection.

12:02

20 THE WITNESS: In that -- he is not talking  
21 about selectivity there. He is just talking about  
22 sensitivity.

23 BY MR. LIPSEY:

24 Q There is no reference to non-specific  
25 amplification, is there, in that sentence?

1           A    Well, the next sentence takes up the question,  
2           again.

3           Q    But in that first sentence, there is no  
4           reference --

5           A    It says, "This can be achieved by non-specific  
6           replication using standard enzymes." That's the  
12:02 7           sentence referring to that sentence that you read, the  
8           very next sentence.

9           Q    The first sentence of the paragraph says  
10          nothing about non-specific amplification, correct?

11          A    You're not supposed to read one sentence in a  
12          patent and take it out of context unless you're a  
13          really, you know, disgraceful patent lawyer, you read  
14          the whole things. The very next sentence talks about  
15          non-specific amplification, doesn't it? And it says the  
16          way you would do that is by non-specific replication  
17          using standard enzymes.

18                        So it's kind of -- it has no meaning at all to  
19          say this one sentence there is no reference non-specific  
12:03 20          amplification, where if, in fact, in that same paragraph  
21          that sentence is referred to with a description of sort  
22          of a further description of what he is talking about and  
23          it says non-specific.

24          Q    We'll come back to that in just a minute  
25          because I know you have some views on that and I'd like

1 to hear what they are.

2 Would you turn to column 32, please.

3 Do you see there in Claim 1 talks about a  
4 method for amplifying a target polynucleotide? Do you  
12:03 5 see that?

6 A Yes.

7 Q And step C is amplifying the target  
8 polynucleotide?

9 A That's right.

10 Q There is no reference to non-specific  
11 amplification there, is there?

12 MR. SWINTON: Same objection.

13 THE WITNESS: Not in 1 (c).

14 By MR. LIPSEY:

15 Q Okay. Now, going back --

16 A I think it's common for claims to refer back to  
17 the examples in a sentence. You're supposed to  
18 interpret the claims in light of the examples and also  
19 the specifications. They don't stand by themselves.  
12:04 20 There is no way to understand what he is talking about  
21 right there without looking back at the rest of the  
22 patent to find out what he did.

23 Q Okay, let's go back and talk about that.

24 Let's go back to column 30 of the '338 patent,  
25 Plaintiff's Exhibit 5. And specifically to the

90

12:04 1 penultimate sentence before example 4, starting at about  
2 line 38. The text states there "Thus no specially  
3 tailored primers are needed for each test and the same  
4 standard amplification reagents can be used regardless  
5 of the targets." Do you see where I've read?

6 A I see it.

7 Q You understood that reference to specially  
8 tailored primers to be a reference to specific primers  
9 of the sort used in specific amplification techniques,  
10 correct?

11 A Yes.

12 Q And further up, starting at about line 32,  
13 well, starting at line 30 it says, "Amplification of the  
14 target nucleic acid sequences, because it follows  
15 purification of the target sequences, can employ  
16 non-specific enzymes or primers." Do you see where I've  
17 read?

18 A I see that.

19 Q The alternative to non-specific enzymes and  
20 primers is specific enzymes and primers, correct?

21 A Well, you might have non-specific enzymes and  
22 specific primers or you could have a lot of other  
23 alternatives, but that is one of them.

24 Q Okay. Now, I think in your expert report you  
12:06 25 indicated that it can be an awful lot of work to

1 actually design a specific primer for use in PCR; is  
2 that right?

3 A Did I say it would be an awful lot of work?

4 Q Could be an awful lot of work.

5 A I'd like to see that. I don't remember doing  
6 an awful lot of work to do that. It's a process that is  
7 pretty much done by computers now. Did I say --

12:06 8 Q Would you turn to page 11 of your expert  
12:07 9 report, Defendant's Exhibit 198, please.

10 You're talking about in the first paragraph  
11 about the process of designing primers for use in PCR.  
12 And you indicate all of the factors that need to be  
13 taken into consideration in designing that primer, do  
14 you see that?

15 A Right.

16 Q And then you say it's common for scientists to  
12:07 17 design, test and then redesign and retest sequence  
18 specific primers?

19 A If you're setting up a -- if you're going to  
20 set up reactions, as you do very often, you want to  
21 optimize all kinds of things. That would be one of the  
22 things you -- I didn't say anything about a lot of work  
23 there.

24 Q I mean, in fact, some of your early experiments  
25 failed because you hadn't properly designed the primer,

1 right?

12:08 2 A Well, which of my experiments failed? I'm not  
3 sure what you're talking about here. Failed in what  
4 sense? Failed in not amplifying the things that I  
5 wanted?

6 Q Right.

7 A The only one I think we've seen reference to  
8 where it didn't get the needle in the haystack thing is  
9 where I was running the reaction -- I was suggesting  
10 don't run it at a cold temperature, you're causing --  
11 you're shooting yourself in the foot. But there is no  
12 doubt that you can have better and better specificity by  
13 finding just that right combination of primers. I  
14 didn't say anything about how much work it was. But, I  
15 mean, you can, you can spend a lot of time on it if you  
16 want to. Usually the first two you pick work.

17 Q Well --

18 A That's usually the case.

19 Q Well, which is it? Is it a trivial matter?

20 A Usually the first two that you pick work, okay?  
21 If you're going to be doing a reaction many, many times  
22 and you want to find the very best set of primers, then  
23 you could -- you can shop around and find different ones  
24 and say -- compare them all to each other and say which  
12:09 25 is the best.

1           And that's what you would do if you're setting  
2 up like a routine laboratory procedure for, you know --  
3 like if you're looking for some organism that is going  
4 to happen -- that you're going to have lots and lots of  
5 applications for that particular thing, then you might  
6 spend a lot of time doing it. Usually the first pair of  
7 primers that you pick, however, get you a result that  
8 will be useful in that -- in the average situations.

9           People don't spend a lot of time. They have  
10 little computer programs that basically try to match the  
12:09 11 melting temperature of both primers by using the little  
12 equation that gives you that, and if you -- you put a  
13 pair of primers together and they don't give you the  
14 result that you're wanting, that is usually the  
15 exception, and then you might want to alter them because  
16 maybe those primers are amplifying a sequence that  
17 actually has those primers in it, but you just didn't  
18 know about that sequence. That sometimes can happen.

19           There is not a lot -- there is nothing in there  
20 that says it's a lot of work. I believe you were saying  
12:10 21 it was a lot of work.

22           Q    You did not mean in the sentence where you  
23 wrote, "It is come on for scientists to design, test and  
24 then redesign and retest sequence specific primers to  
25 achieve effective sequence specific amplification of a

1 desired target sequence," you did not intend by that to  
2 suggest by that it was a lot of work; is that your  
3 testimony?

4 A Actually, I'll read you what I said. I said,  
5 "Designing specific primers requires some knowledge of  
6 the intended target sequence," okay, that's not a lot of  
7 work yet, is it, "and often requires laboratory testing  
12:10 8 to determine if the sequence specific primers, in fact,  
9 function in a sequence specific manner to amplify the  
10 intended target sequence."

11 So you have to do an experiment. That's what  
12 you're going to do anyhow if you're going to use them,  
13 right? And if it works the first time, no work has  
14 actually been expended selecting targets. If you want  
15 to optimize a reaction for more and more strenuous  
16 conditions, you might do a little bit more, you put a  
17 little more effort into that.

18 But I'm not sure what the point is that you're  
19 trying to make. Is it -- you know, when this patent was  
12:11 20 first applied for, you could say, hey, it takes a lot of  
21 effort to synthesize oligos. It is not the way it is  
22 now, and it's not they way it was when I wrote this.

23 Q By "this patent," did you mean your patent?

24 A No, the `338 there, those people felt like  
25 there was a need -- that it was -- they thought it was a



1 real pain to have to synthesize primers. They also were  
2 operating under another constraint, we might add, in  
3 that they knew they couldn't get away with using two  
4 specific primers because that was already patented. So  
5 they were trying to get around that patent by saying  
12:11 6 here is another way to achieve the same result as PCR  
7 does without doing PCR. That is the intention of these  
8 people.

9 And then they say, "Now, well, look how cool  
10 this is," they have to show utility, so they say, "Here  
11 is a way to do that without even having to synthesize  
12 the primers." But we know what they're talking about,  
13 don't we?

14 Q Well, let me -- let me --

15 A Were they suffering from having to synthesize  
12:12 16 primers, or were they just trying to come up with  
17 another way to amplify sequences that wouldn't be  
18 subject to the '202 patent? That's what they were  
19 doing. They weren't having a problem synthesizing  
20 oligodes by then. There were machines.

21 Q So a benefit of combining target capture with  
22 amplification is that it becomes possible to do an assay  
23 that doesn't infringe your patent?

12:12 24 A Theoretically, although I have not seen any --

25 MR. SWINTON: Vague -- I'm sorry, vague as to

1 the definition of "amplification." Incomplete  
2 hypothetical.

3 MR. LIPSEY: You may answer.

4 THE WITNESS: Repeat the question again because  
5 I want to make sure of what you said.

6 BY MR. LIPSEY:

7 Q So a benefit of combining target capture with  
8 amplification in an assay is that it becomes possible to  
9 conduct that assay in a way that wouldn't infringe your  
10 '202 patent, right?

11 MR. SWINTON: Same objection.

12 THE WITNESS: I think that was the point here  
13 was to try to figure out a way to amplify -- although we  
2:13 14 also know it didn't work. But Amoco is used to dry  
15 holes, aren't we? I mean, it didn't work in any  
16 practical sense. It said it did, but it didn't. Nobody  
17 has used it.

18 BY MR. LIPSEY:

19 Q Well, have you done any experiments? Have you  
20 duplicated any of the experiments in the patent?

21 A No.

22 Q Do you know anybody that has?

23 A I don't know anybody that does non-specific  
24 amplification now for a living.

25 Q Okay. That --

1 A Can't find anything in the literature about  
2 that.

12:13

3 Q We've covered a lot of ground here. I want to  
4 touch on all of it, but let's do it in a systematic  
5 way. Let's go back to the paragraph on page 11 of your  
6 report, Exhibit 198.

7 In that whole discussion of the process of  
8 designing primers and figuring out what the reaction  
9 conditions and what not are, under which they'll  
10 hybridize, were you meaning to suggest there that that  
11 process was beyond the capabilities of people working in  
12 this field in December of 1987?

12:14

13 A Well, it was harder than it is now. Now you're  
14 just -- you get a computer program, there is computer  
15 programs freely available on the net that do that all  
16 the time. What are you -- I'm not sure what your  
17 question is, we did that in a sense, but not as well as  
18 we can do it today because we have more sequences  
19 available.

20 Q But the experimentation needed to make the  
21 primers and get them to work is something that people  
22 knew how to do in December of 1987; is that right?

12:14

23 A They didn't always know exactly what all of the  
24 factors were, but they knew how to do the experiments  
25 empirically and test a set of primers in the situation

1 that they would be used and find out whether they  
2 worked.

3 Q Okay.

4 A We did that.

5 Q Okay. Fair enough.

6 And, in fact, that's something you have to do  
12:15 7 in order to do PCR each time also, right?

8 A You have to get -- use the right sequences of  
9 your primer. You have to know the sequences you're  
10 going to amplify. That kind of goes without saying,  
11 doesn't it?

12 Q Now --

13 A Things like oligonucleotides melting  
14 temperature, sequence composition, those are things that  
15 weren't all that clear in 1987 but have come clear  
16 since, and they're now approached with computer programs  
17 that can calculate melting temperatures and get the both  
12:15 18 primers matched up. You also have access to the  
19 database, the human genome, so you can look and see if  
20 there are other fragments that might amplify with those.

21 Q But those matters going to questions of primer  
22 design and selecting hybridization conditions were  
23 sufficiently well known in December of 1987 for people  
24 to do PCR, right?

25 A Yes.

1 Q Now, let's take a look at Example 5 of the '338  
?:16 2 patent, which is Plaintiff's Exhibit 5. Why don't you  
12:16 3 take a -- well, you've read this and read it recently, I  
4 gather; is that right?

5 A I haven't read it recently. I read it some  
6 time ago.

7 Q Why don't you take a moment and read it.

12:17 8 A Okay.

12:17 9 Q Okay. Now, in that example, once the denatured  
10 target DNA is isolated and then made double stranded,  
11 the RNA polymerase basically functions to make many  
12 copies of the RNA transcript of that DNA, correct?

12:18 13 A Right.

14 Q And one way of making that isolated denatured  
15 target DNA double stranded described here is by use of  
16 random primers, right?

17 MR. SWINTON: Objection; argumentative, vague  
18 as to "one way." The document speaks for itself.

12:18 19 THE WITNESS: One way to attempt to do that  
20 would be to use random primers, although that's -- it's  
21 kind of strange that they say that makes it double  
22 stranded because most of it still ends up being single  
23 stranded. It doesn't work the same way when do you it  
24 with specific primers as it does when you do it with  
25 non-specific ones, because it makes many different

1 molecules that overlap sometimes and become double  
2 stranded but which have not the same ends necessarily.  
3 Do you see the difference there.

4 That gives you some double stranded character,  
12:19 5 which they in this case would like to have because the  
6 RNA polymerase in their eyes only acts on double  
7 stranded sequences, but they're wrong there too because  
8 it will act on a single stranded sequence, but that's  
9 what they're trying to accomplish.

10 Q Okay. The example goes on to state,  
11 "Alternatively, the double stranded DNA can be formed by  
12 synthesis starting from Capture Probe A," do you see  
12:19 13 that?

14 A Yes.

15 Q Now, Capture Probe A is a specific  
16 oligonucleotide primer, correct?

17 A Yes, that's the one they wanted to use for the  
18 probe.

19 Q So if one follows that approach, then the only  
20 double stranded DNA in the system is DNA to which that  
21 capture probe specifically bound, correct?

22 MR. SWINTON: Incomplete hypothetical.

12:20 23 THE WITNESS: Yes. It actually -- to do it  
24 this way would probably lead to more specificity than to  
25 do it with the random hexamers. You've already got it

1 hanging there, you might as well extend it on them. AS  
2 long as you don't do it twice, you don't get in trouble  
3 with the '202.

4 BY MR. LIPSEY:

5 Q What do you mean by that?

6 A Well, if you put another primer on the other  
7 end and do it, do it again with that one, now you've got  
8 PCR.

9 Q But, in fact, you could do it repeatedly with  
12:20 10 that single capture probe and get specific linear  
11 amplification, right?

12 MR. SWINTON: Argumentative --

13 THE WITNESS: Specific, in the sense of more  
14 specific than doing it with the hexamers, but certainly  
15 not specific in regard to -- with respect to doing it  
16 with two different oligos that both had to be involved.  
17 That's a very big difference. It's a difference like 10  
18 to the 7th and 10 to the 14th, which is a big  
19 difference. It's lots of zeros. That's why I was  
12:21 20 talking early there are levels of specificity, and  
21 certainly, this particular example would lead -- would  
22 probably lead to a more specific -- a more specific  
23 amplification than just the one where you know for sure  
24 it isn't specific.

25 This one, also, you could repeat, like you're

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1 saying, you could do it, melt it off, do it again, melt  
2 it off, do it again, and you would get a linear  
3 amplification that was more specific than just  
4 amplifying everything.

5 BY MR. LIPSEY:

6 Q If we now look at Example 7, why don't you take  
12:21 7 a moment and look at that again. This is in the '338  
8 patent, Plaintiff's Exhibit 5.

12:22 9 A You want me to read the claims?

12:22 10 Q No, just Example 7.

11 A Okay. I'm done with that.

12 Q Okay. There is reference there to an in vitro  
13 exponential amplification method.

14 A The Q-Beta-replicase things, right.

15 Q But the property of it is described as being in  
16 vitro, and it's said to replicate exponentially.

17 A Yes.

18 Q Now, if I told you in December of 1987 to use  
19 an in vitro method of exponential amplification, what is  
12:23 20 the first thing that would have come to mind?

21 MR. SWINTON: Objection; incomplete  
22 hypothetical.

23 THE WITNESS: If you told me in 1987, what  
24 would come to my mind?

25 BY MR. LIPSEY:



1 Q Yes.

2 A I would say I do it every day.

3 Q PCR?

4 A Um-hum.

5 Q Okay.

6 A If you told me to use the Q-Beta-replicase to  
7 achieve it, I would laugh at you, however.

12:23 8 Q You would just look at that and know it  
9 wouldn't work, is that what you're saying?

10 A I would look at the -- at that point there was  
11 some literature available on Q-Beta-replicase system,  
12 and it never was practical to use it in any kind of a  
13 diagnostic situation. It was interesting from a  
14 molecular biological standpoint, looked nice on paper  
15 too, maybe to lawyers, but it didn't work. It didn't  
16 work for the purpose of making a specific target, making  
12:24 17 copies of a specific target.

18 Q And --

19 A They didn't try to do that here either. They  
20 don't use the replication as a form of specificity.  
21 They just use it as a form of replication.

22 Q I mean, are you suggesting you could have  
23 looked at that thing in December of 1987 and known it  
24 wouldn't work?

25 A Q-Beta-replicase, to do a specific -- to

12:24

1 amplify a specific sequence, knowing what I knew in '87,  
2 the Q-Beta-replicase system had been around probably for  
3 about 10 years, but it was looked at as a -- people  
4 talked about it sometimes for its ability to amplify  
5 things, but people had not practically used it.

6 People, you know, had been working on the  
7 problem of trying to detect DNA sequences before PCR,  
8 and this was one of the things mentioned back there  
9 somewhere I'm sure in JBC papers and stuff, but not in a  
10 practical way.

11 Nobody around Cetus, for instance, who was  
12 working on this problem tried the Q-Beta-replicase thing  
13 before PCR, and they certainly wouldn't have afterward.  
14 But even before, when we were dealing with very low  
15 target levels, this -- that was a pretty fanciful way to  
16 go about it. It didn't work in the way -- it did not --  
17 there was nothing in there that had to do with  
18 selectivity or specificity. It's just it had to do with  
19 total sample amount. There are two subjects, how much  
20 of it have you got, and is it in the presence of so much  
21 other stuff that you can't see it? Those are separate  
22 issues.

12:25

23 But the Q-Beta-replicase didn't really relate  
24 to the issue of how do you separate your particular  
25 sequence from all of the rest of them.

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1 Q But if you could have separated your sequence  
2 from all of the rest of them, would you have understood  
3 the Q-Beta-replicase could have made many, many, many  
4 copies of that isolated sequence?

5 MR. SWINTON: Incomplete hypothetical, vague as  
6 to time, beyond the scope of his opinion.

7 THE WITNESS: I would have understood that it  
8 could have made a lot of copies of itself and some  
12:26 9 sequence attached to it, and there were technical  
10 difficulties there that I wouldn't have tried to use  
11 that. I would have tried to think of a better method,  
12 and I did. But, I mean, I don't know what you're trying  
13 to prove.

14 Are you saying if you had a single sequence and  
15 you somehow attached it, put it into the Q-beta system,  
16 then could that thing amplify just that -- it amplifies  
17 that, it also amplifies a lot of other sequences related  
18 to itself. You know, the Q-beta has to replicate its  
12:26 19 own self in addition to replicating the sequence that  
20 you've sort of fooled it with.

21 Q Okay. I'm actually just trying to get your  
22 view as to whether somebody reading that Example 7 in  
23 December of 1987 would have concluded that on its face  
24 it wouldn't have worked as described there.

25 MR. SWINTON: Objection; beyond the scope of

1 his opinion, incomplete hypothetical.

2 THE WITNESS: I don't know about somebody else,  
3 but when I see an example like that that doesn't contain  
12:27 4 any detail and no results, I would say I bet they didn't  
5 even try it.

6 MR. LIPSEY: That wasn't quite my question.

7 THE WITNESS: Well, I would have said it  
8 probably won't work either because I know about this.  
9 Here Blumenthal describing this when, '79? I mean,  
10 there was -- there were papers out there about the  
11 Q-Beta-replicase system because it was a curious thing.

12 MR. LIPSEY: Why don't we break for lunch.

13 THE VIDEOGRAPHER: Off the record at 12:27.

2:28 14 (Lunch recess.)

13:26 15 THE VIDEOGRAPHER: On the record at 1:26.

16 BY MR. LIPSEY:

17 Q Dr. Mullis, could you take out your expert  
18 report, Defendant's Exhibit 198, please.

19 A Okay.

20 Q Would you turn to the second page, please.

21 There in the first paragraph, you refer to your  
13:27 22 understanding about the Doctrine of Equivalents, do you  
23 see that?

24 A Right.

25 Q From whence did you derive your understanding?

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1           A    From, I guess, Bill Bowen probably explained  
2   that to me.

3           Q    Further down on the page under the heading  
4   "Nucleic Acid Amplification," you refer to probes there  
5   in the first paragraph, do you see that?

6           A    Right.

7           Q    In this field, I guess in December of '87,  
8   since that's the time we're talking about, when people  
13:27 9   referred to probes in nucleic acid assays, what  
10   generally did that mean?

11          A    It's the same still. It would be like -- a  
12   probe for nucleic acids would be a complimentary --  
13   nucleic acids was complimentary to a sequence that you  
14   were trying to detect, so it would attach itself  
15   specifically to it, and a probe usually carries some  
16   sort of signal, like it to could be a flourescent thing,  
13:28 17   or it could be radioactively labeled, something like  
18   that, so it allows you to locate and detect a particular  
19   sequence.

20          Q    Would you turn to page 5, please. The third  
21   line there you state in part, "Generally practical in  
22   vitro amplification methods use two primers." Do you  
13:28 23   see that?

24          A    Yes.

25          Q    What are the alternatives to using two primers?

1 MR. SWINTON: Incomplete hypothetical, vague.  
2 Alternatives to what?

3 THE WITNESS: You know, I probably could have  
4 stated that a -- I could have said forget about the  
5 "generally." I could have just said "Practical in vitro  
6 amplification methods use two primers." So, I mean,  
7 you're asking me what else would there be and my -- I  
13:29 8 would have to say that there probably isn't any -- I  
9 don't know of any at least widely used other methods.  
10 So generally is maybe not the right way to phrase that.

11 BY MR. LIPSEY:

12 Q Well, I think we talked earlier about what  
13 happens when you use only one primer; do you remember  
14 that?

15 A You could use -- yeah, it's true, but there is  
13:29 16 like -- you could -- you could -- like to make a  
17 sequencing, like a template for sequencing, I think  
18 these days sometimes they don't amplify. First they do  
19 that sort of -- it looks like PCR when you're doing it,  
20 because you're doing it in one of their machines, but  
21 you only have one primer in there, and you just run  
22 about 10 cycles or 20 cycles, and it makes a single  
23 stranded template that makes it real easy to sequence.

24 Q In each one of those cycles it would make one  
13:30 25 more copy of the template?

1 A One more copy.

2 Q So at the end of the cycle, you would have 20  
3 more copies of the template?

4 A I guess generally was the right word there --

5 Q I thought that was what you meant. I just  
6 didn't know if you had something else in mind.

7 Would you turn to page 6, please. Now, in this  
8 section of your report, you deal with the question of  
13:30 9 whether specific and non-specific amplification methods  
10 perform substantially the same function; is that right?

11 A Yes.

12 Q Now, in your discussion -- well, maybe we can  
13 short circuit this. Later on you analyze whether or not  
14 they perform in the same way. Do you remember that  
15 generally?

13:31 16 A Yes.

17 Q And then I think you talk about whether or not  
18 they obtain the same result later in the report.

19 A Um-hum.

20 Q In connection with all of those analyses, do  
21 you mention the impact of separating the target nucleic  
22 acid from other nucleic acids in the sample before  
23 amplification?

24 MR. SWINTON: Best evidence, irrelevant, beyond  
25 the scope of his opinion.

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13:31

1

THE WITNESS: I'm not certain that I understand the question that you're asking me, so --

2

3

BY MR. LIPSEY:

4

Q I mean, it seemed to me reading your report that you were comparing and contrasting specific and non-specific amplification generally and not necessarily comparing and contrasting specific and non-specific amplification in the context of a process where the target nucleotide had already been isolated from the sample; is that right?

5

6

7

8

9

13:32

10

11

MR. SWINTON: Same objections.

12

THE WITNESS: I may have been. I mean, I was talking about specific and non-specific amplification methods, and I was trying to describe what that meant and not the entire processes that might be used in.

13

14

15

16

BY MR. LIPSEY:

17

13:32

18

19

20

Q Okay. Would you turn to page 7, please. Now, here we're still talking about whether specific and non-specific amplification performed the same function, right, that's the heading on the prior page?

21

A Um-hum.

22

13:33

23

24

25

Q And you state at the bottom, "If one amplifies non-specifically the amount of the nucleic acid in the entire sample may have been increased to the point that it is impossible to analyze it, even if the amount of

111



1 the target sequence has been increased to detectable  
2 levels," do you see that?

3 A Yeah.

4 Q Okay. What did you mean by that?

5 A Well, if you -- let's say you're trying to --  
6 you have a tube that has got, say -- maybe it's got a  
13:33 7 Microgram of DNA total in it, of which maybe a millionth  
8 of that or a picogram of that is the sequence that  
9 you're interested in. Now, if you -- if you need to  
10 have like, say, a thousand picograms of this sequence  
11 that you're interested in in order to detect it, and you  
12 try to produce that by making a thousand copies of every  
13 single thing that is in there, you're going to end up  
14 with a thousand micrograms of total DNA in the tube, and  
13:34 15 you can't put a thousand micrograms of total DNA on most  
16 of the detection systems that one would use to detect a  
17 thousand -- I mean, like a thousand picograms of a  
18 single sequence. It's just physically impossible.

19 So it says you could have it there, but you  
20 can't really -- you can't stick it -- you can't put it  
21 into a mass spectrometer, you can't put it onto an  
22 electrophoretic gel, you can't really probe it in the  
13:34 23 presence of all that DNA that you've made. You haven't  
24 really helped yourself a lot if you're trying to find  
25 something specific just by amplifying up everything in

1 general. That should be self-evident.

2 Q Now I understand what you meant.

3 I'd like the reporter to mark as identification  
4 Defendant's Deposition Exhibit 211 one of the documents  
5 that Dr. Mullis brought with him this morning, which  
13:35 6 appears to be a copy of page 7 of his expert report with  
7 some handwritten notes. I'm sorry, a copy of his  
8 declaration.

9 (Defendant's Exhibit 211 was marked for  
10 identification by the court reporter.)

11 BY MR. LIPSEY:

12 Q The paragraph we've been talking about in your  
13:35 13 expert report, Defendant's Exhibit 198, appears here as  
14 paragraph 20 of this declaration; is that right?

15 A Okay.

16 MR. SWINTON: Could I see the entirety of the  
17 document from which this was extracted.

18 MR. LIPSEY: Sure.

19 MR. SWINTON: Could you pull it out so I don't  
20 have to fumble through.

21 MR. LIPSEY: My fumbling is the same as your  
22 fumbling.

23 MR. SWINTON: If you're fumbling, at least  
24 you're not asking a question that I have to try to  
25 listen to at the same time. So one of us can't do two

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13:36

1

things at once.

2

MR. LIPSEY: It's right there. In fact, if you would like to show the witness the original, I have no objection to that.

5

Are you ready?

6

MR. SWINTON: He has offered if you want to see the original, it's there. I've seen it for my purposes.

13:36

7

8

BY MR. LIPSEY:

9

Q Okay. Just to get us started here, this paragraph No. 20 on Defendant's Exhibit 211 appears to correspond to the paragraph on the bottom of page 7 of your expert report; do you agree with that?

10

11

12

13

A I think so. I mean, do you want me to read it?

14

Q I haven't read it word for word, but it --

15

A It ends and begins the same so hopefully the middle is the same too.

13:37

16

17

Q Now, the handwriting on the side of Exhibit 211 is whose?

18

19

A That's mine, and I think that was probably yesterday.

20

21

Q Can you read into the record what you've written there.

22

23

A "The chances of finding a needle in a haystack are not necessarily improved by multiplying the needle and the haystack to many needles and many haystacks,"

24

25

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1 and then I said sort of a colon I think is that  
2 punctuation mark, sort of like saying thus,  
13:37 3 "non-specific amplification doesn't improve your chances  
4 of finding a needle in a haystack."

5 Q Okay. And that is, in more laymen friendly  
6 words, the point you were making in that paragraph 20?

7 A Right. If you're trying to find your car, for  
8 instance, in a big parking lot, it won't do you any good  
9 to have every car in the parking lot duplicate itself a  
10 few times. You still have to search through the same  
11 number of cars to find yours. But if you have your car  
12 duplicate itself a few times and the rest of the cars  
13:38 13 just stay like they are, you have a better chance of  
14 finding your car.

15 Q To stick with your needle in the haystack  
16 analogy, if you took the needle out of the haystack  
17 first --

18 A Then you've already found it.

19 MR. SWINTON: You have to -- I have an  
20 objection and we have to let him finish the question.

21 BY MR. LIPSEY:

22 Q -- and then multiplied the needle, you could  
23 help yourself out in terms of detecting the needle,  
24 right?

25 MR. SWINTON: Objection; relevance, beyond the

1 scope of his opinion, incomplete hypothetical.

2 THE WITNESS: I was -- I'm only talking about  
3 the amplification process itself. I'm not talking about  
13:38 4 some other way of specifically identifying the thing.  
5 If you want me to address that, I can. I mean, it is  
6 within my range of knowledge. I'm not saying that if  
7 you really could do that, that it might not work  
8 sometimes. In my opinion, actually, you know, the  
9 methods that are described in this patent, they haven't  
10 ever worked anywhere well enough to have been of note to  
11 anyone.

12 But I'm not saying absolutely that they  
13 wouldn't do something at some time. I'm not saying  
14 that. But I'm saying the amplification part of it,  
15 taken separately doesn't improve your chances just to  
16 make more of it, if you make more of everything that is  
17 in the way.

18 See, I mean, if you want to identify something  
19 in somebody's blood stream, right, that's a lot easier,  
20 there is nothing stopping you from taking 10 milliliters  
21 of blood instead of a tenth of a milliliter of blood.  
22 It's just that you don't really have any better chance  
23 of discovering some minute quantity of something in  
13:39 24 someone's blood by just taking more of it, because it's  
25 the background that is the problem, and non-specific

1 amplification doesn't solve that problem.

2 Now, if you can solve that with some other  
3 method, then maybe the non-specific amplification --  
4 once you have the thing isolated by itself, maybe the  
5 non-specific amplification will help you bring that up  
6 to a level of detectability.

7 Although, as I mentioned before, when we  
8 started talking about where linear amplifications may be  
9 used right now, the limit of detectability these days is  
10 pretty low. So, I mean, non-specific amplification  
11 doesn't really have much role to play, as far as I'm  
12 concerned, in any -- didn't in 19- -- didn't in 1987 or  
13 whenever this thing was first patented, and it doesn't  
14 now. It's never been used because it doesn't. You're  
15 beating a dead horse here.

16 BY MR. LIPSEY:

17 Q How many copies of a target polynucleotide can  
18 you make using non-specific amplification, if you know?

19 MR. SWINTON: Incomplete hypothetical, beyond  
20 the scope of his opinion.

21 THE WITNESS: How many do I think you could  
22 make?

23 BY MR. LIPSEY:

24 Q Yeah?

25 A I really, like I said earlier, I haven't had

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1 any direct personal experience with it, but it depends  
2 on -- you know, it depends on how small a fraction of  
3 the sample you're dealing with is actually the target  
4 that you're interested in. If it's very -- if it's a  
13:41 5 lot of it there in the first place compared to the  
6 background, then maybe you can do yourself some good by  
7 amplifying the whole mixture, maybe.

8 But as you -- every time you -- if you start --  
9 think of a mixture might be a million different things.  
10 Every step of amplification is going to create another  
11 million things, right, instead of just another one or  
12 two or four or eight or whatever of the one you want.  
13 If you have to make a million every time, then you have  
14 two million things, and then have you to amplify.

13:41 15 Just to get another two copies of the thing  
16 you're looking for, you have to make four million  
17 things, and eventually that just fills up the space and  
18 uses up all the reagents. The enzymes can only work at  
19 a certain rate. You know, it just -- it's a losing  
20 proposition.

21 Q Would you turn to page 9 of your report,  
13:42 22 Defendant's Exhibit 198. You make the statement there  
23 in the bottom paragraph starting in the second line,  
24 that "TMA and PCR may result in some very limited amount  
13:42 25 of amplification of non-target sequences." Do you see

1 where I've read?

2 A Yes.

3 Q Do you have any information as to whether TMA  
4 is more specific or less specific than PCR?

5 A It's -- if PCR is practiced as is currently --  
6 after about 1987 was with a thermostabile polymerase so  
7 the reactions can be run under very high specificity,  
13:43 8 TMA, in my experience -- which can't be because some of  
9 the enzymes are labile to heat -- is about a million  
10 times less specific.

11 Q And that's why Gen-Probe needs to use target  
12 capture prior to TMA amplification; is that right?

13 MR. SWINTON: Argumentative, lacks foundation,  
14 beyond the scope.

15 THE WITNESS: I wasn't involved in that work,  
16 so I'm not sure, but, you know, that's a reasonable  
13:43 17 inference that they need to have some other step in  
18 there if they don't have a method of amplification.  
19 Depends on what they're looking for, and I don't know  
20 what products they're trying to develop, but it makes  
21 sense to me that that's why they probably --

22 MR. LIPSEY: I'd like the reporter to mark for  
23 identification as Defendant's Deposition Exhibit 212 a  
24 November 1, 2001 e-mail from Stephen Swinton to Kary and  
13:44 25 Nancy, who I presume are Kary and Nancy Mullis.

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1 (Defendant's Exhibit 212 was marked for  
2 identification by the court reporter.)

3 BY MR. LIPSEY:

4 Q Okay. What is Exhibit 212?

5 A It's just like you described it, it looks like  
6 an e-mail from Steve to me and Nancy.

7 Q Okay. And --

13:44 8 A And then I've written some stuff on the bottom  
9 of it there just because it was laying on the desk top.

10 Q Okay. And this e-mail was yesterday, right?

11 A Yes, I think it was.

12 Q Okay. And you've been talking to Mr. Swinton  
13 yesterday and today, right?

14 A Right but this -- I say this little piece of  
15 paper, it wasn't like addressed to him necessarily. It  
16 was just on the table in front of me.

17 Q But it was on the table in front of you during  
18 your conversations with Mr. Swinton, right?

19 A No. I think I wrote this just before the game  
13:45 20 started last night, something like that, and it was just  
21 sitting there, and I had a pencil in my hand, and I  
22 wrote that on it.

23 Q The handwriting is yours?

24 A That's mine.

25 Q Would you read into the record what you've

1 written in the box there at the bottom.

2 A "TMA is not quite as specific as PCR thus the  
3 need for prepurification. But if non-specific  
4 amplification is not that different from specific  
5 amplification, what is all of the excitement about. (As  
6 in the Nobel Prize)" that sort of thing.

13:45 7 I mean, somebody knows, besides me and you out  
8 there, that specific amplification is the ticket, right?  
9 It's the thing that transformed molecular biology. It  
10 is not, you know, the non-specific amplification methods  
11 that were proposed prior to PCR of being able to do  
12 something like that. Those didn't work.

13 There is a big difference. Regardless of what  
14 you may think about it, there is a big difference in a  
15 practical sense. You can't do all of the tricky things  
13:46 16 you can do with PCR with non-specific -- non-specific  
17 amplifications, even if you use target capture methods.  
18 It's been shown by experiment.

19 Those people that wrote these patents didn't  
20 make any products that made any money. It's ridiculous  
21 that you're trying to say well, because of that this is  
22 a great invention, and it also includes everything else  
23 that has been done in DNA chemistry since this. It's  
24 like, what an incredibly horrible thing to have to  
25 defend. I feel sorry for you.

13:46

1

Q Well, we'll see in the end, Dr. Mullis. You

2

should feel sorry for one of us, I will go that far.

3

But referring back to what you read -- I'm

4

afraid your answer is a little incomplete. The part

5

that is in your handwriting on Exhibit 212 that is in

6

the box that you've drawn at the bottom says "TMA is not

7

quite as specific as PCR thus the need for

13:47

8

prepurification," did I read that correctly?

9

A That is my speculation, because I really wasn't

10

there when they were designing that system, but that

11

made sense to me. I said, this is probably why they

12

wanted a prepurification of some sort, a sequence

13

directed prepurification, you know, and I put the box

14

around there later. I wrote it all as one paragraph, so

15

that's why I decided to read it. I don't like taking

16

things out of context.

17

Q Just by prepurification, you're referring to

13:47

18

the target capture step, right?

19

A Yes, something like that.

20

Q And the box you drew is around that first

21

sentence?

22

A The box I drew is certainly around it, but I

23

also had written the other stuff underneath it.

24

Q Would you turn to page 13, please. The second

13:48

25

complete paragraph there, the second sentence says, "For

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1 example, Gen-Probe's amplification method generally uses  
2 two primers." Do you see that?

13:48

3 A Yes.

4 Q Okay. My question is the same as the one I  
5 asked earlier, which is, under what circumstances would  
6 Gen-Probe's method use something other than two primers?

7 A You know, I think I've been a little liberal  
8 with the word generally. I think my familiarity with  
9 their method is it always uses two primers.

13:49

10 Q Would you turn to page 14, please. You may  
11 wish to read the paragraph surrounding this to get the  
12 context to answer my question.

13 In the middle of that first paragraph on page  
14 14 you make the statement, "The T7 RNA Polymerase does  
15 not amplify other sequences present in the sample  
16 because they are not attached to a T7 promoter  
17 sequence." Do you see that?

18 A Yes.

13:49

19 Q Now, in point of fact, in the Gen-Probe  
20 assays, the target sequence has been separated from the  
21 other nucleic acids in the sample prior to association  
22 of the T7 promoter sequence with it; isn't that right?

23 A Well, I'm not sure exactly how they do it,  
24 I'll trust you on that one, but you can start this sort  
25 of procedure, which I, by the way, invented a long time

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1 ago, this same thing that they call TMA right now, and  
2 you can start that with a nucleic acid that hasn't been  
3 prepurified, and the promoter sequence attaches itself  
4 specifically by sequence to the target sequence.

5 Because one end of that primer is the promoter sequence  
6 which is general for T7, and the other part of it is the  
7 specific sequence that brings that in to the sequence  
8 you want to amplify.

9 Q But as far as you know in the TMA -- in the  
10 process used in the Gen-Probe assays, the T7 promoter  
11 sequence is not associated with the target sequence  
12 until after it's been separated from the sample; is that  
13 right?

14 A I -- I'm just saying I haven't looked at the  
15 instructions on their kit, but that makes sense if they  
16 want to prepurify it and then do the TMA procedure,  
17 that's what would happen.

18 Q Okay. In your opinion, had there been in  
19 December of 1987 a technique for detecting a nucleic  
20 acid in a sample that employed specific amplification as  
21 by PCR, would it have been obvious to substitute in that  
22 technique non-specific amplification?

23 MR. SWINTON: Beyond the scope of his opinion,  
24 incomplete hypothetical, calls for a legal conclusion,  
25 vague as to "obvious."

1 BY MR. LIPSEY:

2 Q But other than that, a fine question.

3 A It might have been obvious to you. It wouldn't  
4 have been obvious to me. You know, I knew the ropes  
5 there and I said no, why would you? I mean, what would  
6 you hope to accomplish by that? It's the same -- it's a  
7 different thing altogether, isn't it?

13:52 8 Q I'd like the reporter to mark for  
13:53 9 identification as Defendant's Deposition Exhibit 213 a  
10 January 23, 2001 draft that appears to have been  
13:53 11 prepared by Dr. Mullis, but we will find out.

12 (Defendant's Exhibit 213 was marked for  
13 identification by the court reporter.)

14 BY MR. LIPSEY:

15 Q First of all, have you seen Defendant's  
16 Deposition Exhibit 213 before?

17 A Me? Have I seen this?

13:54 18 Q Yes.

19 A Yes.

20 Q What is it?

21 A It's like a note that I probably sent to Bill  
22 while we were, you know, discussing all of these issues  
23 and I was reading the patents and stuff like that.

24 Q By Bill, you mean Bill Bowen, counsel for  
25 Gen-Probe?

1 A Yes, Bill Bowen.

2 Q This bears the date January 23, 2001. Is it  
3 your belief that is about the time it was prepared?

4 A Yes, I imagine it was.

5 Q And the first paragraph starts off by talking  
13:54 6 about the invention described in the '338 patent; do you  
7 see that?

8 A Yes.

9 Q Is it your belief that you had the '338 patent  
10 at that time?

11 A Yes.

12 Q Now, in bold in the center of the first page,  
13 you've got an entry with the heading "But Look At This"  
3:55 14 with multiple exclamation marks; do you see that?

15 A Yeah.

16 Q In bold you describe a -- well, you state  
17 "People were and still are snatching mRNAs out of  
18 extracts with oligo-dT-cellulose every day, eluting  
19 them, and then doing RT-PCR on them." Do you see where  
20 I've read?

21 A Yes.

22 Q Okay. Now, what does RT-PCR mean in that  
13:55 23 context?

24 A It means when you want to start a PCR reaction  
25 from an RNA instead of from a DNA, you do reverse

1 transcriptase first. It's like a --

2 Q Okay, but RT-PCR as used there is a specific  
3 exponential amplification technique?

13:56

4 A Yeah, it's a PCR reaction where the first step  
5 is to convert an RNA to a DNA, and after that it's the  
6 same thing as just a normal PCR.

7 Q Then two sentences after that, you state, "I  
8 think this fairly common process reads directly on Claim  
9 1, A, B and C," double exclamation mark. Do you see  
10 where I've read?

3:56

11 A Yes. I'm referring to the fact that I don't  
12 think -- it looks to me like what is actually -- why was  
13 this patent issued is kind of what I was suggesting. It  
14 seems like people were already doing something similar  
15 enough that it fell within those claims, and therefore  
16 those claims probably shouldn't have been allowed.

17 Q And your reference there to Claim 1 A, B and C  
18 is to Claim 1 of the '338 patent?

19 A Of the '338, yeah.

20 Q That's Plaintiff's Exhibit 5, right?

21 A Of which?

22 Q I think it's right over there.

23 A Okay. That would have been what I was talking  
24 about.

25 Q The A, B and C are reference to the

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1 subparagraph in Claim 1; is that right?

3:57

2 A Excuse me?

3 Q The A, B and C in Defendant's Exhibit 213 are  
4 references to the subparagraphs A, B and C in Claim 1?

5 A Yeah, that's the whole claim, Claim 1 A, B, C.

6 Q And subparagraph C in the claim calls for the  
7 step of amplifying the target polynucleotide; is that  
8 right?

9 A Um-hum.

10 Q Okay. And then you go on to say -- having said  
13:57 11 that you think this fairly common process reads directly  
12 on Claim 1 A, B and C you then say, "also Claims 2-5,  
13 7-11 and all their derivatives," do you see that?

14 A Yeah, I'm saying 2 through 5 and 7 through  
15 whatever, right, I see that.

16 Q But that's intended to be a reference to 2  
17 through 5 and 7 to 11?

18 A 2 through 5, 7 through 11.

19 Q Of the '338 patent?

13:58 20 A And the various ones that are derivative on  
21 those claims, I guess.

22 Q But of the '338 patent?

23 A Yes.

24 Q I'd like the reporter to mark for  
25 identification --

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1 MR. SWINTON: Before you get to the next one, I  
2 have to take a personal break for about two minutes so  
3 let's go off the record.

4 THE VIDEOGRAPHER: This is the end of tape  
5 number 2 of Volume 1. We're off the record at 1:58.

13:59 6 (Recess.)

14:02 7 THE VIDEOGRAPHER: This is the beginning of  
14:02 8 tape number 3, Volume 1. We're on the record at 2:02.

9 MR. LIPSEY: I'd like the reporter to mark for  
10 identification as Defendant's Deposition Exhibit 214  
11 what appears to be an e-mail from Bill Bowen to  
12 Dr. Mullis dated March 27, 2001.

14:03 13 (Defendant's Exhibit 214 was marked for  
14 identification by the court reporter.)

15 BY MR. LIPSEY:

16 Q Have you seen Exhibit 214 before?

17 A Yes, I have.

18 Q What is it?

19 A Well, it's exactly what you said, it's an  
20 e-mail from Bill Bowen to me.

21 Q Is it your belief it was sent to you on or  
22 about March 27, 2001?

23 A Yes.

24 Q Okay. So that would have been after your  
25 e-mail which we marked as Exhibit 213, right?

1 A Right.

2 Q Okay. Now, in the last paragraph on the first  
14:03 3 page, Mr. Bowen states "In order to support our  
4 position, we'll need a declaration from an expert  
5 witness that if one of skill in the art read the '338  
6 patent, he would understand the inventors to teach a  
7 method of amplification using non-specific primers." Do  
8 you see where I've read?

9 A Wait a minute, where is that on this page?  
10 Okay. Okay.

14:04 11 Q Did you discuss with Mr. Bowen the possibility  
12 of preparing and filing such a declaration?

13 A Did I discuss with him the possibility of  
14 filing such a declaration?

15 Q Yes, of your filing such a declaration.

16 A You know, I must have on the phone, I probably  
17 said, "Sure, I can do that."

18 Q Did you, in fact, file such a declaration?

14:04 19 A Well, I -- maybe I didn't actually. I'm not  
20 sure if I did.

21 Q Okay. I mean, such a declaration was prepared,  
22 but you did not, in fact, sign and file it; is that  
23 right?

24 A No. I don't think I decided not to. I still  
25 agreed with that notion. That's what that -- that's

1 what all of the examples in the patent described, and  
2 the patent was very specific about the fact that, "Hey,  
3 we've got this great method where you don't need  
14:05 4 specific primers. You don't need to synthesize them."  
5 So I think if he would have asked me to sign something  
6 that says that, I would have gladly signed it.

7 Have you seen such a thing that I didn't sign?  
8 I mean, I didn't read something and say, "No, Bill, I  
9 can't sign this." Usually if I didn't like the wording  
10 or something, I would come back with my own wording or  
11 something. If he asked me specifically to sign  
12 something that said that, I would have said sure.

13 Q Well, let me see if I can refresh your  
14:05 14 recollection. I'd like the reporter to mark for  
15 identification as Defendant's Deposition Exhibit 215 a  
16 draft declaration of Dr. Joseph Falkinham prepared in  
17 connection with this case.

14:06 18 (Defendant's Exhibit 215 was marked for  
19 identification by the court reporter.)

20 BY MR. LIPSEY:

21 Q Do you see this draft declaration on the very  
22 back page is prepared for signature in April of 2001?  
23 Do you see that? It's on the very last page of the  
24 exhibit.

25 A It says --

1 Q Right at the bottom of the text it says April  
2 2001.

1:06

3 A Mine says "This declaration was executed by me  
4 on this blank day of April, Joseph O. Falkinham."

5 Q Right, so the draft declaration, 215, on its  
6 face indicates it was prepared for signature in April  
7 2001, right? That's the date on the back?

8 A Okay, you're reading that off the front of  
9 this?

10 Q No, I was reading it off the same thing you  
11 just read on the last page.

14:07

12 A Maybe I'm going to have to put on my glasses  
13 here. I'm not seeing that. What line is that on?

14 Q The very last line of text before the  
15 signature.

16 A "This declaration was executed by me on this  
17 blank date of April 2001, at blank," is that what you  
18 want?

19 Q Right.

20 A I misunderstood what you were saying.

21 Q Exhibit 215 appears -- at least on its face  
22 appears to have been prepared for signature after the  
23 e-mail to you in March of 2001, which we've marked as  
24 Exhibit 214, correct?

14:07

25 MR. SWINTON: Objection; lacks foundation.

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THE WITNESS: I agree.

BY MR. LIPSEY:

Q And why don't you read the summary of the opinion in paragraph 4 on the second page of Exhibit 215.

A Okay.

14:08

Q Now, the opinion expressed here is "Reading the specification," of the '338 patent, "a person of ordinary skill in the art would not have understood the term 'amplifying' as used in the claims of the '338 patent to mean amplifying by use of sequence-specific amplification methods." Do you see that?

A Yes.

Q Were you asked to sign such a declaration?

14:08

A Well, I would have, and I would now, but I don't recall -- I certainly didn't decline to do that. I didn't say, "No, take this to somebody else, I can't do it," because I've certainly expressed that opinion in a couple of other things, I believe.

Q But in the spring of 2001, the March, April, May time frame --

A I would have had the same opinion.

Q -- you did not sign such a declaration, did you?

MR. SWINTON: Asked and answered. We'll

1 stipulate that. Same answer you gave before when he  
1:09 2 asked you.

3 THE WITNESS: I would say I didn't -- as far as  
4 I know, I didn't. But I didn't -- Bill didn't send me  
5 something and say, "Could you sign this," and I said no  
6 and he sent it to Falkinham. That didn't happen, as far  
7 as I know. I never saw -- you know, maybe -- I was  
8 traveling a whole lot this year, and he may have said,  
9 "Well, Falkinham will do it. You don't have to do it."  
10 Any idiot could do that actually. It doesn't require a  
11 rocket scientist.

12 MR. SWINTON: On behalf of Dr. Falkinham, I  
14:09 13 respectfully object, but go ahead.

14 THE WITNESS: The examples in the patent  
15 clearly are non-specific amplification examples. They  
16 crow about the fact that you can get away with that and  
17 that's what they're inventing, so why wouldn't somebody  
18 sign something like that?

19 BY MR. LIPSEY:

20 Q Okay. But this particular declaration was, in  
21 fact, prepared for your signature?

22 A It was?

23 Q Wasn't it?

24 A I -- frankly, I don't know. I mean, am I  
25 supposed to know that?

1 MR. SWINTON: Argumentative, assumes facts not  
2 in evidence.

3 THE WITNESS: This whole declaration that Randy  
14:10 4 signed was made for me?

5 BY MR. LIPSEY:

6 Q That's what I'm asking.

7 A Or Joseph -- I don't think so. I certainly did  
8 not look this over and say "Get somebody else; I won't  
9 do it."

10 Q Okay. Would you turn to page 8 of the  
11 declaration. And specifically to paragraph 33. First  
12 sentence there reads in part, "The amplification process  
13 described in Example 6 and illustrated in Figure 6 is a  
14 cycling method similar to the cycles of synthesis used  
14:10 14 in the PCR method that I invented." Do you see that?

15 A Yeah, I see that.

16 Q Okay, now Dr. Falkinham didn't invent PCR,  
17 right?  
18

19 A Not that I know of. But, you know -- so maybe  
20 when he started writing this, he had that in mind, and  
21 he just didn't go back and change it when he decided  
22 "I'll get Falkinham to do it." But it did not -- there  
23 is no -- I didn't refuse to sign this and then he did  
24 that. I may have been gone for three weeks or something  
14:11 25 like that and he got Randy to do it or maybe -- I don't

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1 know, but I mean -- I certainly don't disagree with this  
2 thing, and I didn't at the time.

3 Q I'd like to go back to Defendant's Deposition  
4 Exhibit 213. That's your January 23, 2001 e-mail. Do  
14:11 5 you have that?

6 A Okay, got it.

7 Q And you refer there to the '338 patent and  
8 specifically to the combination of target capture with  
14:12 9 amplification as by Q-Beta-replicase referred to as we  
10 saw in Example 7 of the '338 patent that is Plaintiff's  
11 Exhibit 5, right?

12 A Yes.

13 Q And you've stated at the end of that paragraph  
14 "Nonetheless, some variant of this method could have  
15 obviously been employed prior to a specific nucleic acid  
16 amplification such as the polymerase chain reaction."

14:12 17 Did I read that correctly?

18 A Yes.

19 Q Now, moving down to the block portion that we  
20 talked about before under the heading "But Look At  
21 This," you refer there to people snatching mRNAs out of  
22 extracts with oligo-dT-cellulose and eluting them.

23 A Um-hum.

24 Q Is that a reference to the process of isolating  
14:13 25 all of the messenger RNA in a sample?

1 A Yes.

2 Q And that process works because all of the  
3 messenger RNA has polyA tails on the end of it, right?

4 A Right.

5 MR. SWINTON: Beyond of scope of his opinion,  
6 incomplete hypothetical.

7 BY MR. LIPSEY:

8 Q And by -- the polyA tails will stick to the  
9 poly T (phonetic) on the cellulose and thereby separate  
10 the messenger RNA from --

14:13 11 A The rest of the nucleic acid, in particular,  
12 the ribosomal RNA, which is the thing you're really  
13 trying to get rid of there.

14 MR. SWINTON: Same objection.

15 BY MR. LIPSEY:

16 Q How many different mRNA species are present in  
17 a clinical sample?

18 MR. SWINTON: Incomplete hypothetical.

19 THE WITNESS: Nobody knows, actually, but we  
20 know it's probably less than 260,000, something like  
21 that because --

14:14 22 BY MR. LIPSEY:

23 Q But it could be as high as 260,000?

24 A It could be as high as 260. It's generally --  
25 people would -- I think most people would estimate less

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1 in any particular cell type. You know, if you took --  
2 that would be a lot of genes expressing themselves all  
3 at the same time.

4 Q How much less? I mean, what would people say  
5 is the number of different mRNA species in a clinical  
6 sample?

7 MR. SWINTON: Beyond of scope of opinion,  
8 incomplete hypothetical.

9 THE WITNESS: If you were to say how many of  
10 them are in there at levels of more than, say, 30,000  
14:14 11 copies per cell or something that would be a question --  
12 nobody would reasonably ask the question that you asked  
13 if they understood --

14 BY MR. LIPSEY:

15 Q Let's start with my question, and then we'll  
16 answer your question.

17 How many different mRNA species are there in a  
18 clinical sample.

19 MR. SWINTON: Objection. Beyond the scope,  
14:15 20 incomplete hypothetical, beyond the scope of his  
21 opinion.

22 I'm sorry, Dr. Mullis, go head.

23 THE WITNESS: The question kind of doesn't  
24 really make sense because they're all in different  
25 states of -- there is a whole lot of different ones, we

1 know that, a whole lot.

2 BY MR. LIPSEY:

3 Q Okay.

4 A For any particular type of one, there is a lot  
5 of them that are freshly made with a nice polyA tail.  
6 There is a few of them that have just a little less tail  
7 and a little less and a little less. There are some of  
14:15 8 them that are torn up by various things. So they aren't  
9 things in the sense of like bbs in a jar, they're all  
10 different states of similar stuff.

11 Then there is high level expression of RNAs and  
12 there is low, and there is very low, and there is almost  
13 nonexistent. If you try to count all of the different  
14 RNA species in a cell, you would be dealing with  
15 something that is probably not a rational number. It's  
16 probably something that is harder to define than how  
17 many. I'm not sure where your question is headed.  
14:16 18 There is a lot of them.

19 Q I mean thousands?

20 A Thousands is probably -- but if you look at  
21 the -- like, if you look at experiments that sort of  
22 relate to that kind of thing where you just, say, make  
23 cDNA clones of every single one of them that you can get  
24 through a system, like that poly oligo-dT thing, clone  
25 everything, and look at how many different clones you

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1 have, which is not often done, because you have to count  
2 them separately, see how many of them are different.  
3 There is no probe for one that is there just once, but  
4 there are experiments that relate to that, and the  
14:16 5 answer is probably that at any one time in any one cell  
6 line, there is probably 20,000 different species of  
7 RNA there in an amount that is significant enough to  
8 where you can look at it.

9 But I've never seen an experiment that really  
10 goes to that exactly. In the experiments that do try,  
11 they have -- you know, it's like the things they do at  
12 Affymetrix, the things they do at Encyte, where they say  
13 what are the levels of like 1400 different ones that we  
14 have probes for here, and we put them on this little  
15 array and we look at them. That's not really asking the  
14:17 16 question, how many are there, that's just saying of the  
17 ones we have probes for, how many of them are there and  
18 in what amount.

19 But I would estimate that that would be -- you  
20 know, I don't think most of my colleagues would doubt --  
21 they would say, "Yeah, that's probably as good a guess  
22 as anybody." What do you need to know for?

23 Q I was just curious, and I've got you here to  
24 ask.

25 A Well, it would matter what you need to for

1 know, you say "Because of this" and I say, "Well, this  
2 would be a good number for that particular purpose."

14:17 3 Q Okay. Now, this technique that you refer to of  
4 snatching all of the mRNA out of an extract using  
5 oligo-dT, that technique was used in some of the most  
6 famous experiments in molecular biology; isn't that  
7 right?

8 MR. SWINTON: Beyond the scope of his opinion.

9 THE WITNESS: That's beyond the scope of  
10 opinion. But it's been certainly around for a long  
11 time, and a lot of people use that. If you want to pull  
12 out mRNA.

13 BY MR. LIPSEY:

14 Q It was used in the first cloning of a human  
14:18 15 gene -- or excuse me, the first cloning of a mammalian  
16 gene, wasn't it, back in the '70s?

17 MR. SWINTON: Beyond the scope.

18 THE WITNESS: I believe you're right, it was  
19 used in -- virtually everybody that works with RNA  
20 probably has oligo-dT in his pocket somewhere.

21 BY MR. LIPSEY:

22 Q Well, in fact, some of the most famous  
23 experiments at the very beginning of molecular biology  
24 involved isolation of messenger RNA on an oligo-dT  
14:18 25 column, reverse transcribing it into cDNA and cloning it

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1 in vivo, right?

2 A Yeah.

3 MR. SWINTON: Beyond the scope.

4 THE WITNESS: Therefore, I don't understand why  
5 this patent was ever issued, because that does seem to  
6 fall under the -- that's what I said to Bill, I said,  
7 "How could they possibly have issued this patent?" I  
8 mean, generally interpreting those claims would include  
9 that. And that was already quite well known in the  
10 literature before 1987, so "What is the deal here,  
11 Bill?"

14:19

12 BY MR. LIPSEY:

13 Q Anybody who had a Ph.D. degree in molecular  
14 biology or related science would know about those early  
15 experiments; isn't that right?

16 MR. SWINTON: Beyond the scope of his opinion,  
17 incomplete hypothetical, lacks foundation.

18 THE WITNESS: Apparently Gary Jones didn't have  
19 a Ph.D. or didn't know that, huh?

20 BY MR. LIPSEY:

21 Q What about Diane Reese?

22 A Maybe Diane didn't know about that either.

23 MR. SWINTON: Same objections.

24 MR. LIPSEY: Can we take a short break.

14:19

25 THE VIDEOGRAPHER: Off the record at 2:19.

14:20 1

(Recess.)

1:26 2

THE VIDEOGRAPHER: On the record at 2:27.

14:27 3

MR. LIPSEY: Dr. Mullis, Vysis has no further questions for you at this time subject to the requests we've made of your counsel for additional information. Thank you very much for taking the time to come down and talk to us.

8

MR. SWINTON: I think I have only one question.

14:27 9

EXAMINATION

10

BY MR. SWINTON:

11

Q Dr. Mullis, my question, the only question I have for you really relates in part to some of the commentary of the questions that Mr. Lipsey has asked you, that are at least reflected in part by the questions he asked associated with Exhibit 212. Those were the notes that you placed on a document that happened to be an e-mail that I had sent you the other day. Do you remember that?

14:28 18

19

A Yeah.

20

Q The only question I have for you is this: Have you had any interaction with anyone at Gen-Probe -- scientists or technical person or lawyer -- by which you learned from them, in fact, why Gen-Probe may use a target capture step in conjunction with TMA?

25

A No, I haven't actually had -- I mean, that was

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1 just -- I was sort of thinking myself, what would be,  
2 why are they do this? I didn't get that from any -- I  
14:28 3 hadn't ever talked to anybody there, I think, at all.

4 MR. SWINTON: No further questions.

5 FURTHER EXAMINATION

6 BY MR. LIPSEY:

7 Q Dr. Mullis, just one point. In connection with  
8 your activities as a potential expert for Gen-Probe, you  
9 have had continuing contact with employees of Gen-Probe  
14:29 10 and lawyers for Gen-Probe for more than a year; is that  
11 right?

12 MR. SWINTON: Assumes facts not in evidence.

13 THE WITNESS: The only person I've had contact  
14 with that I know is the Gen-Probe employee would be Bill  
15 Bowen, who is the lawyer. I haven't been down there to  
16 see them. I haven't talked to anybody else. Bill is  
17 the only person I've really had contact with at all.

14:29 18 BY MR. LIPSEY:

19 Q Okay. But Mr. Bowen is both an employee and a  
20 lawyer at Gen-Probe, right?

21 A Yes, so I've talked to him.

22 Q And you've had extensive discussions and  
23 correspondence with him relating to the issues in this  
24 case for more than a year; is that right?

25 MR. SWINTON: Argumentative as to "extensive."

1 THE WITNESS: Whatever, I mean, I've talked to  
2 him about this for over a year, as I mentioned.

3 MR. LIPSEY: Okay, we have no further  
4 questions. Thank you.

5 MR. SWINTON: Nothing further.

14:30 6 THE VIDEOGRAPHER: This is the end of tape No.  
7 3 of Volume 1 and concludes the deposition --

8 MR. SWINTON: Why don't we take the video  
9 record off and save a little bit of -- and we'll --  
10 we'll memorialize the stipulation that we ought to be  
11 able to use for all of our experts, I assume.

12 I propose, Charlie, that for all of the experts  
13 we use the same scenario we did, I think, for the fact  
14 witnesses.

15 If you will provide the original deposition to  
14:30 16 me, I'll ensure that Dr. Mullis signs it, reviews it,  
17 signs it under penalty of perjury and we'll provide you  
18 with any corrections that may be made to that.

19 MR. LIPSEY: Is there a customary time frame on  
20 that just --

21 MR. SWINTON: Only if -- expedited only if  
22 you're paying for it.

23 MR. LIPSEY: I'm saying in terms of your  
24 providing --

25 MR. SWINTON: What have we been doing, 30 days?

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MR. BURWELL: 30 days, is that going to give us enough time?

MR. LIPSEY: Well --

MR. SWINTON: He is not -- I don't know what you're planning to do anyway for a hearing, but I doubt -- I'm not going to be in a position to agree that Dr. Mullis would see something in the next day that you have prepared and sign it. If you need a stipulation, do whatever you intend to do with the draft, I'll reserve my objections, and at least within 30 days after receipt Dr. Mullis will sign it.

MR. LIPSEY: Fair enough.

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I, KARY B. MULLIS, Ph.D., do hereby declare under penalty of perjury that I have read the foregoing transcript; that I have made such corrections as noted herein, in ink, initialed by me, or attached hereto; that my testimony as contained herein, as corrected, is true and correct.

EXECUTED this \_\_\_\_ day of \_\_\_\_\_,  
2001, at \_\_\_\_\_, \_\_\_\_\_.  
(City) (State)

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KARY B. MULLIS, Ph.D.

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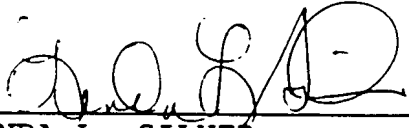
I, the undersigned, a Certified Shorthand Reporter of the State of California, do hereby certify:

That the foregoing proceedings were taken before me at the time and place herein set forth; that any witnesses in the foregoing proceedings, prior to testifying, were placed under oath; that a verbatim record of the proceedings was made by me using machine shorthand which was thereafter transcribed under my direction; further, that the foregoing is an accurate transcription thereof.

I further certify that I am neither financially interested in the action nor a relative or employee of any attorney of any of the parties.

IN WITNESS WHEREOF, I have this date subscribed my name.

Dated: NOV 03 2001

  
\_\_\_\_\_  
LINDA L. SILVER  
CSR No. 9915